

01-776

## SEARCH REQUEST FORM

Requestor's

Name:

Jeffrey E. Russel

Serial

Number:

PCT/US98/25964

Date:

1-26-1999

Phone:

308-3975

Art Unit:

1654

9807

## Search Topic:

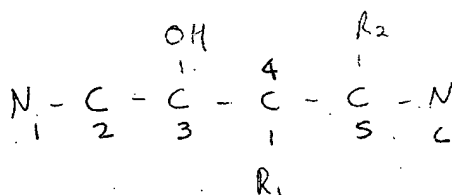
Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).

Please search the partial structures below and attached.


Keywords are HIV and protease inhibitor.

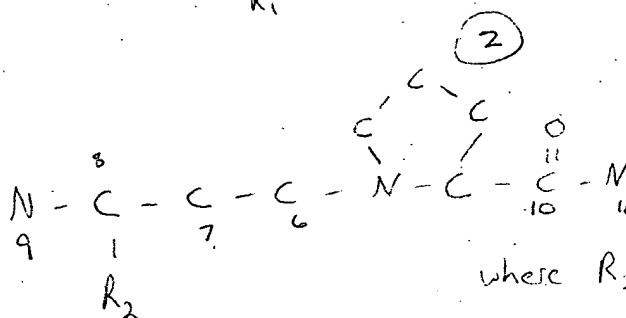
Thank you.


JER



where R1 = H or OH

R2 = alkyl or -CH2-



where R2 = alkyl or -CH2-

810.65 C5

## STAFF USE ONLY

Date completed: 01-29-99  
Searcher: Beverly @ 4994  
Terminal time: 40  
Elapsed time: \_\_\_\_\_  
CPU time: \_\_\_\_\_  
Total time: 55  
Number of Searches: \_\_\_\_\_  
Number of Databases: 1

## Search Site

☐ STIC☐ CM-1☐ Pre-S

## Type of Search

☐ N.A. Sequence☐ A.A. Sequence☐ Structure☐ Bibliographic

## Vendors

☐ IG☒ STN☐ Dialog☐ APS☐ Geninfo☐ SDC☐ DARC/Questel☐ Other

PCT/25964

FILE 'REGISTRY' ENTERED AT 12:05:55 ON 29 JAN 1999  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
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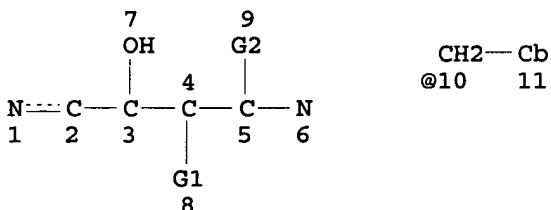
STRUCTURE FILE UPDATES: 23 JAN 99 HIGHEST RN 217939-24-7  
DICTIONARY FILE UPDATES: 28 JAN 99 HIGHEST RN 217939-24-7

TSCA INFORMATION NOW CURRENT THROUGH JUNE 29, 1998

Please note that search-term pricing does apply when  
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=> d que stat; fil caplu; s l6 or l6/d

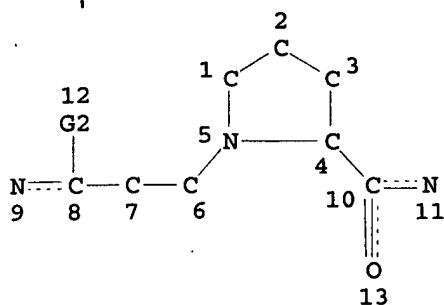
L1 STR



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GGCAT IS UNS AT 11  
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE  
L2 STR



CH<sub>2</sub>—Cb  
@14 15

Str. 2

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NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

GGCAT IS UNS AT 15

DEFAULT ECLEVEL IS LIMITED

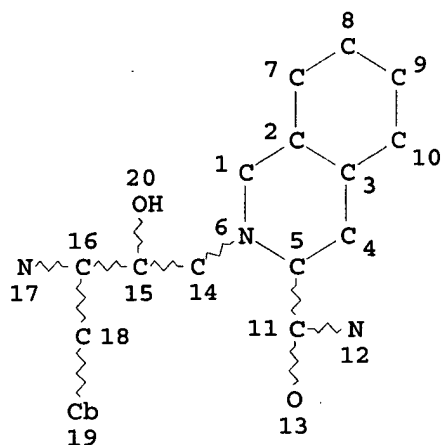
GRAPH ATTRIBUTES:

RSPEC I

NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE

L3 STR



Str. 3

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

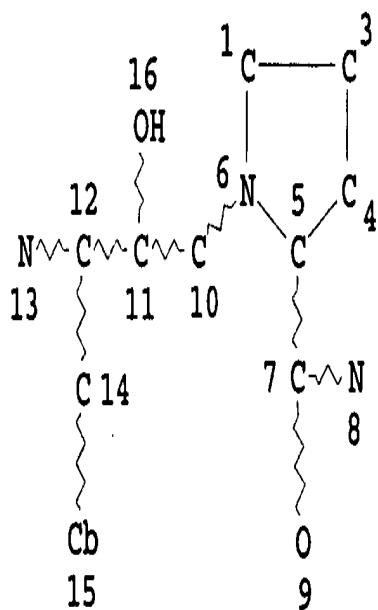
RSPEC I

NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE

L4

STR



str. 4

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

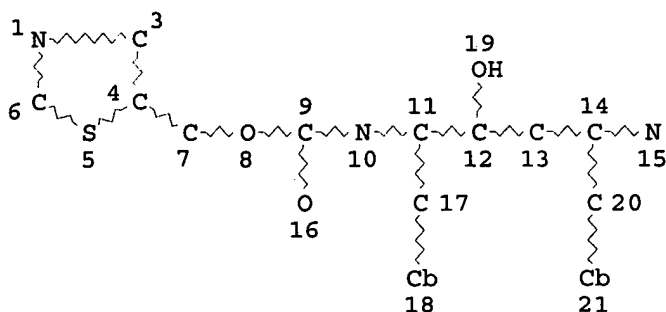
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE

L5

STR

Searcher : Shears 308-4994



Str. 5

## NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

## GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 20

## STEREO ATTRIBUTES: NONE

L6 2575 SEA FILE=REGISTRY SSS FUL L1 OR L2 OR L3 OR L4 OR L5

Temp saved 7 days.

100.0% PROCESSED 172527 ITERATIONS

2575 ANSWERS

SEARCH TIME: 00.01.42

FILE 'CAPLUS' ENTERED AT 12:09:01 ON 29 JAN 1999

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FILE COVERS 1967 - 29 Jan 1999 VOL 130 ISS 5

FILE LAST UPDATED: 29 Jan 1999 (19990129/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REGISTRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

Searcher : Shears 308-4994

565 L6  
 24 L6/D  
 L7 565 L6 OR L6/D  
 L8 1764 SEA ABB=ON PLU=ON ((PROTEINASE OR PROTEASE) (W) INHIBIT?)  
 (3A) (FIV# OR HIV# OR HTLV# OR (HUMAN OR FELINE) (3W) VIRUS?  
 OR IMMUN? (1W) VIRUS? OR AIDS OR ACQUIR? (2W) SYNDROM?)  
 L9 82 SEA ABB=ON PLU=ON L7 (3A) L8

=> d 1-82 .bevstr

L9 ANSWER 1 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1999:23648 CAPLUS  
 TI Development of HIV protease inhibitors. A survey  
 AU Ren, Shijun; Lien, Eric J.  
 CS Dep. Pharmaceutical Sciences, School Pharmacy, Univ. Southern  
 California, Los Angeles, CA, 90033, USA  
 SO Prog. Drug Res. (1998), 51, 1-31  
 CODEN: FAZMAE; ISSN: 0071-786X  
 PB Birkhaeuser Verlag  
 DT Journal; General Review  
 LA English  
 AB A review with 63 refs., describing the development of human  
 immunodeficiency virus (HIV) protease inhibitors as antiviral agents  
 against HIV, structure-activity relationship anal. of saquinavir and  
 related compds., comparison of the HIV protease inhibitors  
 saquinavir, ritonavir, indinavir, and nelfinavir, and future  
 prospect in developing new anti-HIV drugs.  
 IT 127779-20-8, Saquinavir 155213-67-5, Ritonavir  
 RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological  
 study); USES (Uses)  
 (development of HIV protease  
 inhibitors)

L9 ANSWER 2 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1998:674195 CAPLUS  
 TI Protease inhibitors and adipocyte differentiation in cell culture  
 AU Gagnon, AnneMarie; Angel, Jonathan B.; Sorisky, Alexander  
 CS OGH Research Institute, University of Ottawa, Ottawa, K1Y 4E9, Can.  
 SO Lancet (1998), 352(9133), 1032  
 CODEN: LANCAO; ISSN: 0140-6736  
 PB Lancet Ltd.  
 DT Journal  
 LA English  
 AB The effects of ritonavir and indinavir were tested in the  
 preadipocyte cell line, murine 3T3-L1 cells. Both protease  
 inhibitors enhanced adipogenesis by as much as 10-40%, and  
 Searcher : Shears 308-4994

ritonavir, for reasons unknown, may have a more potent effect. The mechanism by which protease inhibitors induce adipocyte differentiation is not clear. Understanding the adipogenic action of protease inhibitors should help to make their use as anti-HIV agents optimum while keeping side effects on adipose tissue, and perhaps the assocd. deleterious effects on glucose and fat metab. to a min.

IT 155213-67-5, Ritonavir

RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use);

BIOL (Biological study); USES (Uses)

(anti-HIV protease inhibitors and

adipocyte differentiation in 3T3-L1 cell culture)

L9 ANSWER 3 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1998:523635 CAPLUS

DN 129:270017

TI HIV type 1 protease inhibitors fail to inhibit HTLV-I Gag processing in infected cells

AU Pettit, Steven C.; Sanchez, Ricardo; Smith, Terri; Wehbie, Robert; Derse, David; Swanstrom, Ronald

CS Lineberger Comprehensive Cancer, CB7295, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599, USA

SO AIDS Res. Hum. Retroviruses (1998), 14(11), 1007-1014

CODEN: ARHRE7; ISSN: 0889-2229

PB Mary Ann Liebert, Inc.

DT Journal

LA English

AB Protease inhibitors are currently the most effective antiviral agents against human immunodeficiency virus type 1 (HIV-1). In this study we detd. the effect of four HIV-1 protease inhibitors on human T cell leukemia virus type 1 (HTLV-I). Rhesus monkey cells infected with HTLV-I were treated with different concns. of indinavir, saquinavir, ritonavir, or nelfinavir. The effect of these inhibitors was monitored through their effect on the processing efficiency of the viral Gag protein in cells, the natural substrate for the viral protease. The inhibitors failed to block processing of HTLV-I Gag. To confirm these findings, human cells were cotransfected with plasmids encoding infectious copies of HIV-1 and HTLV-I, and the cells were subsequently treated with these same HIV-1 protease inhibitors. At concns. between 5 and 50 times the IC50 for inhibition of HIV-1 replication, inhibition of HIV-1 Gag cleavage was apparent. In contrast, no effect of HTLV-I Gag processing was seen. At higher concns., HIV-1 Gag processing was essentially completely inhibited whereas HTLV-I Gag cleavage was still unaffected. Thus, these inhibitors are not effective inhibitors of HTLV-I Gag processing. Sequence alignments of the HIV-1 and HTLV-I viral proteases and processing sites suggest that the active site of the HTLV-I protease may have subtle differences in substrate recognition compared with the HIV-1 protease.

Searcher : Shears 308-4994

IT 127779-20-8, Saquinavir 155213-67-5, Ritonavir  
 RL: BAC (Biological activity or effector, except adverse); THU  
 (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (HIV type 1 protease inhibitors  
 fail to inhibit HTLV-I Gag processing in infected cells)

L9 ANSWER 4 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1998:446895 CAPLUS  
 DN 129:203171  
 TI HIV-1 Protease Inhibitors Based on Acyclic Carbohydrates  
 AU Zuccarello, Guido; Bouzide, Abderrahim; Kvarnstroem, Ingemar;  
 Niklasson, Gunilla; Svensson, Stefan C. T.; Brisander, Magnus;  
 Danielsson, Helena; Nillroth, Ulrika; Karlen, Anders; Hallberg,  
 Anders; Classon, Bjoern; Samuelsson, Bertil  
 CS Department of Chemistry, Linköping University, Linköping Sweden,  
 S-581 83, Swed.  
 SO J. Org. Chem. (1998), 63(15), 4898-4906  
 CODEN: JOCEAH; ISSN: 0022-3263  
 PB American Chemical Society  
 DT Journal  
 LA English  
 AB A series of acyclic C2-sym. HIV protease inhibitors readily  
 accessible from D-mannitol have been developed. Several of the  
 compds. synthesized showed significant in vitro activity against  
 HIV-1 protease.

IT 211994-23-9P  
 RL: BAC (Biological activity or effector, except adverse); SPN  
 (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (HIV-1 protease inhibitors based on  
 acyclic carbohydrates)

IT 211994-22-8P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)  
 (HIV-1 protease inhibitors based on  
 acyclic carbohydrates)

L9 ANSWER 5 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1998:279538 CAPLUS  
 DN 129:4856  
 TI Syntheses of HIV-protease inhibitors having a peptide moiety which  
 binds to gp120  
 AU Asagarasu, Akira; Uchiyama, Taketo; Achiwa, Kazuo  
 CS Sch. Pharm. Sci., Univ. Shizuoka, Shizuoka, 422, Japan  
 SO Chem. Pharm. Bull. (1998), 46(4), 697-703  
 CODEN: CPBTAL; ISSN: 0009-2363  
 PB Pharmaceutical Society of Japan  
 DT Journal  
 LA English  
 AB Some HIV-protease inhibitor derivs. having an N-carbomethoxycarbonyl-  
 prolyl-phenylalanine benzyl ester (CPF) moiety as a binding site to  
 Searcher : Shears 308-4994



gp120 were designed and synthesized. Almost all the compds. bearing CPF on the phenoxyacetyl group showed protease-inhibitory activity. [[2-(N-methoxalyl-L-prolyl-D-phenylalaninamido)phenoxy]acetyl]-L-asparagyl-[(2S,3S)-3-amino-2-hydroxy-4-phenylbutyryl]-N-tert-butyl-L-proline amide and its m-isomer (25b), which have the CPF moiety at the ortho- and meta-positions of the phenoxyacetyl group, resp., had anti-HIV activity, although the others showed only protease-inhibitory activity. These results suggest that 25b binds to gp120 inhibits HIV protease.

IT 139694-65-8P 153290-12-1P 158221-95-5P  
158221-96-6P 158221-97-7P

RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(syntheses of HIV-protease inhibitors  
having a peptide moiety which binds to gp120)

IT 158221-98-8P 158221-99-9P 158222-03-8P  
158341-23-2P 207444-99-3P 207445-04-3P  
207445-05-4P 207445-06-5P 207445-13-4P  
207445-14-5P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(syntheses of HIV-protease inhibitors  
having a peptide moiety which binds to gp120)

IT 141171-72-4P 207444-84-6P 207444-85-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)

(syntheses of HIV-protease inhibitors  
having a peptide moiety which binds to gp120)

IT 207444-87-9P 207444-88-0P

RL: SPN (Synthetic preparation); PREP (Preparation)

(syntheses of HIV-protease inhibitors  
having a peptide moiety which binds to gp120)

L9 ANSWER 6 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1998:129660 CAPLUS

DN 128:252451

TI HIV-1 Protease Inhibitors Are Substrates for the MDR1 Multidrug  
Transporter

AU Lee, Caroline G. L.; Gottesman, Michael M.; Cardarelli, Carol O.;  
Ramachandra, Muralidhara; Jeang, Kuan-Teh; Ambudkar, Suresh V.;  
Pastan, Ira; Dey, Saibal

CS Laboratory of Cell Biology, National Cancer Institute, Bethesda, MD,  
20892, USA

SO Biochemistry (1998), 37(11), 3594-3601

CODEN: BICHAW; ISSN: 0006-2960

PB American Chemical Society

DT Journal

LA English

OS CJACS

Searcher : Shears 308-4994

AB The FDA approved HIV-1 protease inhibitors, ritonavir, saquinavir, and indinavir, are very effective in inhibiting HIV-1 replication, but their long-term efficacy is unknown. Since in vivo efficacy depends on access of these drugs to intracellular sites where HIV-1 replicates, we detd. whether these protease inhibitors are recognized by the MDR1 multidrug transporter (P-glycoprotein, or P-gp), thereby reducing their intracellular accumulation. In vitro studies in isolated membrane preps. from insect cells infected with MDR1-expressing recombinant baculovirus showed that these inhibitors significantly stimulated P-gp-specific ATPase activity and that this stimulation was inhibited by SDZ PSC 833, a potent inhibitor of P-gp. Furthermore, photoaffinity labeling of P-gp with the substrate analog [125I]iodoarylazidoprazosin (IAAP) was inhibited by all three inhibitors. Cell-based approaches to evaluate the ability of these protease inhibitors to compete for transport of known P-gp substrates showed that all three HIV-1 protease inhibitors were capable of inhibiting the transport of some of the known P-gp substrates but their effects were generally weaker than other documented P-gp modulators such as verapamil or cyclosporin A. Inhibition of HIV-1 replication by all three protease inhibitors was reduced but can be restored by MDR1 inhibitors in cells expressing MDR1. These results indicate that the HIV-1 protease inhibitors are substrates of the human multidrug transporter, suggesting that cells in patients that express the MDR1 transporter will be relatively resistant to the anti-viral effects of the HIV-1 protease inhibitors, and that absorption, excretion, and distribution of these inhibitors in the body may be affected by the multidrug transporter.

IT 127779-20-8, Saquinavir 155213-67-5, Ritonavir  
RL: BPR (Biological process); BIOL (Biological study); PROC  
(Process)  
(HIV-1 protease inhibitors are  
substrates for the MDR1 multidrug transporter)

L9 ANSWER 7 OF 82 CAPLUS COPYRIGHT 1999 ACS  
AN 1998:110766 CAPLUS  
DN 128:225752  
TI Effect of protease inhibitors on nucleoside analog phosphorylation  
in vitro  
AU Hoggard, P. G.; Manion, V.; Barry, M. G.; Back, D. J.  
CS Department of Pharmacology and Therapeutics, University of  
Liverpool, Liverpool, L69 3GE, UK  
SO Br. J. Clin. Pharmacol. (1998), 45(2), 164-167  
CODEN: BCPHBM; ISSN: 0306-5251  
PB Blackwell Science Ltd.  
DT Journal  
LA English  
AB Combination antiretroviral therapy for human immunodeficiency virus  
(HIV) infection now involves both nucleoside analogs and protease  
Searcher : Shears 308-4994

inhibitors. Since intracellular phosphorylation is essential for the activity of all the nucleoside analogs, this study was designed to investigate interactions with protease inhibitors at the intracellular level which may alter antiviral efficacy. PHA-stimulated PBMCs (3.times.10<sup>6</sup> cell/plate) and U937 cells (4.times.10<sup>6</sup> cells/plate) were incubated with either radiolabeled zidovudine (ZDV), stavudine (d4T), zalcitabine (ddC), lamivudine (3TC) or didanosine (ddI) in the presence and absence of the protease inhibitors, indinavir, ritonavir, and saquinavir (0.1-10 .mu.M) for 24 h. Cells were extd. overnight prior to anal. by radiometric h.p.l.c. Intracellular phosphates were standardized to pmol per million cells. None of the three protease inhibitors tested had any significant effect on the intracellular phosphorylation of the five nucleoside analogs. It is particularly important to focus on the active triphosphate anabolites and data for control vs. ritonavir (10 .mu.M) incubations in U937 cells were as follows: ZDVTP, 0.19 vs. 0.21 pmol/10<sup>6</sup> cells (mean .+-. s.d.); d4TTP, 0.30 vs. 0.27; 3TCTP, 0.32 vs. 0.26; ddCTP, 0.07 vs. 0.06; ddATP, 0.014 vs. 0.018 pmol/10<sup>6</sup> cells. The protease inhibitors, indinavir, ritonavir and saquinavir have no effect on the enzymes responsible for phosphorylation. Combining protease inhibitors and nucleoside analogs should not lead to any intracellular interactions in vivo.

- IT 127779-20-8, Saquinavir 155213-67-5, Ritonavir  
 RL: BAC (Biological activity or effector, except adverse); BIOL  
 (Biological study)  
 (effect of HIV protease inhibitors  
 on nucleoside analog phosphorylation in vitro)
- L9 ANSWER 8 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1998:66719 CAPLUS  
 DN 128:162539  
 TI Discovery of Ritonavir, a Potent Inhibitor of HIV Protease with High  
 Oral Bioavailability and Clinical Efficacy  
 AU Kempf, Dale J.; Sham, Hing L.; Marsh, Kennan C.; Flentge, Charles  
 A.; Betebenner, David; Green, Brian E.; McDonald, Edith;  
 Vasavanonda, Sudthida; Saldivar, Ayda; Wideburg, Norman E.; Kati,  
 Warren M.; Ruiz, Lisa; Zhao, Chen; Fino, LynnMarie; Patterson, Jean;  
 Molla, Akhteruzzaman; Plattner, Jacob J.; Norbeck, Daniel W.  
 CS Pharmaceutical Products Division, Abbott Laboratories, Abbott Park,  
 IL, 60064, USA  
 SO J. Med. Chem. (1998), 41(4), 602-617  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CJACS  
 AB The structure-activity studies leading to the potent and clin.  
 efficacious HIV protease inhibitor ritonavir are described.  
 Searcher : Shears 308-4994

Beginning with the moderately potent and orally bioavailable inhibitor A-80987, systematic investigation of peripheral (P3 and P2') heterocyclic groups designed to decrease the rate of hepatic metab. provided analogs with improved pharmacokinetic properties after oral dosing in rats. Replacement of pyridyl groups with thiazoles provided increased chem. stability toward oxidn. while maintaining sufficient aq. soly. for oral absorption. Optimization of hydrophobic interactions with the HIV protease active site produced ritonavir, with excellent in vitro potency ( $EC_{50} = 0.02$   $\mu$ M) and high and sustained plasma concns. after oral administration in 4 species. Details of the discovery and preclin. development of ritonavir are described.

IT 144141-96-8P 144141-97-9P 144142-00-7P  
 144142-01-8P 144142-10-9P 144142-11-0P  
 144142-12-1P 144142-20-1P 144142-66-5P  
 144142-67-6P 144163-01-9P 144163-04-2P  
 144163-05-3P 144163-08-6P 144163-09-7P  
 144163-10-0P 144163-11-1P 144163-12-2P  
 144163-13-3P 144163-16-6P 144163-17-7P  
 144163-18-8P 144163-19-9P 144163-20-2P  
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 144163-28-0P 144185-97-7P 144202-12-0P  
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Searcher : Shears 308-4994

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 202817-02-5P 202817-03-6P

RL: BAC (Biological activity or effector, except adverse); BPR  
 (Biological process); SPN (Synthetic preparation); THU (Therapeutic  
 use); BIOL (Biological study); PREP (Preparation); PROC (Process);  
 USES (Uses)

(prepn. of HIV protease inhibitors  
 with high oral bioavailability and clin. efficacy)

IT 202817-04-7P

RL: BAC (Biological activity or effector, except adverse); SPN  
 (Synthetic preparation); THU (Therapeutic use); BIOL (Biological  
 study); PREP (Preparation); USES (Uses)

(prepn. of HIV protease inhibitors  
 with high oral bioavailability and clin. efficacy)

IT 144163-44-0

RL: RCT (Reactant)

(prepn. of HIV protease inhibitors  
 with high oral bioavailability and clin. efficacy)

IT 144163-26-8P 144164-10-3P 144164-11-4P  
 144186-45-8P 165315-69-5P 165315-78-6P  
 165315-87-7P 165316-37-0P 202817-10-5P  
 202817-12-7P 202817-13-8P 202817-17-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)

(prepn. of HIV protease inhibitors  
 with high oral bioavailability and clin. efficacy)

L9 ANSWER 9 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1998:37615 CAPLUS  
 DN 128:200488

Searcher : Shears 308-4994

- TI Determination of ritonavir, a new HIV protease inhibitor, in biological samples using reversed-phase high-performance liquid chromatography
- AU Marsh, Kennan C.; Eiden, Erin; McDonald, Edith
- CS Pharmaceutical Products Division, Drug Analysis Department, Abbott Laboratories, Abbott Park, IL, 60064, USA
- SO J. Chromatogr., B: Biomed. Sci. Appl. (1997), 704(1 + 2), 307-313  
CODEN: JCBBEF; ISSN: 0378-4347
- PB Elsevier Science B.V.
- DT Journal
- LA English
- AB A simple, accurate and precise HPLC method has been developed for measurement of ritonavir concns. in human plasma. Ritonavir was partitioned from the plasma using liq.-liq. extn. with a mixt. of Et acetate and hexane at neutral pH, with an av. recovery >80%. Following two sequential washings of the reconstituted sample with hexane, chromatog. sepn. was accomplished on a C18 anal. column with a mobile phase contg. acetonitrile, methanol and 0.01 M tetramethylammonium perchlorate in 0.1 aq. trifluoroacetic acid (40:5:55, vol./vol.) with low wavelength UV detection at 205 nm. Std. curves were linear ( $r^2 > 0.9998$ ) over the concn. range 0.01-15  $\mu\text{g/mL}$  with both inter- and intra-day coeffs. of variation typically less than 5. The stability of ritonavir in plasma was excellent, with no evidence of degrdn. after 5 days at room temp. or after 6 mo in a freezer. Decontamination procedures for HIV-pos. plasma samples showed 5.6 and 10.2 degrdn. following heating to 60.degree.C for 30 or 60 min, resp.
- IT 155213-67-5, Ritonavir  
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)  
(detn. of HIV protease inhibitor  
ritonavir in human plasma by HPLC)
- L9 ANSWER 10 OF 82 CAPLUS COPYRIGHT 1999 ACS
- AN 1998:15429 CAPLUS
- DN 128:175813
- TI HIV protease inhibitors, saquinavir, indinavir and ritonavir: inhibition of CYP3A4-mediated metabolism of testosterone and benzoxazinorifamycin, KRM-1648, in human liver microsomes
- AU Inaba, T.; Fischer, N. E.; Riddick, D. S.; Stewart, D. J.; Hidaka, T.
- CS Faculty of Medicine, Department of Pharmacology, University of Toronto, Toronto M5S1A8, Can.
- SO Toxicol. Lett. (1997), 93(2,3), 215-219  
CODEN: TOLED5; ISSN: 0378-4274
- PB Elsevier Science Ireland Ltd.
- DT Journal
- LA English
- AB The protease inhibitors, ritonavir, indinavir and saquinavir, the most potent anti-HIV drugs developed to date, interact with many
- Searcher : Shears 308-4994

drugs by competing for CYP3A4, an enzyme central to the metab. of a wide variety of compds. Human liver microsomes were used to compare inhibition by these three protease inhibitors. The inhibition was the greatest with ritonavir and indinavir and less potent with saquinavir.

IT 127779-20-8, Saquinavir 155213-67-5, Ritonavir  
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(HIV protease inhibitors

(saquinavir and indinavir and ritonavir) and inhibition of cytochrome P 450 3A4-mediated metab. of testosterone and benzoxazinorifamycin (KRM-1648) in human liver microsomes)

L9 ANSWER 11 OF 82 CAPLUS COPYRIGHT 1999 ACS  
AN 1997:812173 CAPLUS  
DN 128:80027  
TI Pediatric formulation for HIV protease inhibitors  
IN Ostovic, Drazen; Thompson, Karen C.  
PA Merck & Co., Inc., USA; Ostovic, Drazen; Thompson, Karen C.  
SO PCT Int. Appl., 22 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9746222	A1	19971211	WO 97-US9109	19970530
	W:				
	AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW:				
	GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9731469	A1	19980105	AU 97-31469	19970530
PRAI	US 96-19097		19960603		
	GB 96-13109		19960621		
	WO 97-US9109		19970530		
AB	Dispersal or suspension of HIV protease inhibitor in glycerol improves palatability and taste for the prepn. of suitable pediatric formulations in the treatment of AIDS, ARC or HIV infection in children and infants. A pharmaceutical suspension contained Crixivan 100, magnasweet 20 g, bubble gum flavor q.s. and glycerol q.s. 1 mL.				

IT 127779-20-8 155213-67-5  
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(pediatric formulation for HIV protease inhibitors)

Searcher : Shears 308-4994

L9 ANSWER 12 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1997:720276 CAPLUS  
 DN 127:302916  
 TI Viracept (Nelfinavir Mesylate, AG1343): A Potent, Orally  
 Bioavailable Inhibitor of HIV-1 Protease  
 AU Kaldor, Stephen W.; Kalish, Vincent J.; Davies, Jay F. ,II; Shetty,  
 Bhasker V.; Fritz, James E.; Appelt, Krzysztof; Burgess, Jeffrey A.;  
 Campanale, Kristina M.; Chirgadze, Nickolay Y.; Clawson, David K.;  
 Dressman, Bruce A.; Hatch, Steven D.; Khalil, Deborah A.; Kosa, Maha  
 B.; Lubbehusen, Penny P.; Muesing, Mark A.; Patick, Amy K.; Reich,  
 Siegfried H.; Su, Kenneth S.; Tatlock, John H.  
 CS Agouron Pharmaceuticals Inc., San Diego, CA, 92121, USA  
 SO J. Med. Chem. (1997), 40(24), 3979-3985  
 CODEN: JMCMAR; ISSN: 0022-2623  
 PB American Chemical Society  
 DT Journal  
 LA English  
 OS CJACS  
 AB Using a combination of iterative structure-based design and an anal.  
 of oral pharmacokinetics and antiviral activity, AG1343 (Viracept,  
 nelfinavir mesylate), a nonpeptidic inhibitor of HIV-1 protease, was  
 identified. AG1343 is a potent enzyme inhibitor ( $K_i = 2$  nM) and  
 antiviral agent (HIV-1 ED<sub>50</sub> = 14 nM). An X-ray cocrystal structure  
 of the enzyme-AG1343 complex reveals how the novel thiophenyl ether  
 and phenol-amide substituents of the inhibitor interact with the S1  
 and S2 subsites of HIV-1 protease, resp. In vivo studies indicate  
 that AG1343 is well absorbed orally in a variety of species and  
 possesses favorable pharmacokinetic properties in humans. AG1343  
 (Viracept) has recently been approved for marketing for the  
 treatment of AIDS.  
 IT 169104-89-6P  
 RL: BAC (Biological activity or effector, except adverse); SPN  
 (Synthetic preparation); THU (Therapeutic use); BIOL (Biological  
 study); PREP (Preparation); USES (Uses)  
 (prepn. of and HIV-1 protease  
 inhibition by viracept and analogs)  
 IT 136522-17-3P 168898-57-5P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. of and HIV-1 protease  
 inhibition by viracept and analogs)  
 L9 ANSWER 13 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1997:438126 CAPLUS  
 DN 127:117088  
 TI Antagonism between human immunodeficiency virus type 1 protease  
 inhibitors indinavir and saquinavir in vitro  
 AU Merrill, Debra P.; Manion, Douglas J.; Chou, Ting-Chao; Hirsch,  
 Martin S.



- CS Infectious Disease Unit, Harvard Medical School, Massachusetts  
General Hospital, Boston, MA, 02114, USA
- SO J. Infect. Dis. (1997), 176(1), 265-268  
CODEN: JIDIAQ; ISSN: 0022-1899
- PB University of Chicago Press
- DT Journal
- LA English
- AB Human immunodeficiency virus type 1 (HIV-1) protease inhibitors are a promising class of antiretroviral agents that compromise enzymic function through substrate mimicry. The in vitro susceptibility of a panel of HIV-1 clin. isolates demonstrating various drug resistance phenotypes to combinations of the HIV-1 protease inhibitors saquinavir and indinavir was detd. Antiviral effect was assessed by an HIV-1 p24 antigen redn. assay in phytohemagglutinin-stimulated peripheral blood mononuclear cells after harvesting of cell-free supernatant fluids at peak antigen prodn. (days 4-7). Drug interactions were detd. by median-dose-effect anal., with the combination index (CI) calcd. at several inhibitory concns. (IC50, IC75, IC90, IC95, IC99). The interactive effects ranged from synergy at low efficacy doses to antagonism at higher doses against a pan-susceptible clin. isolate of HIV-1. Against a zidovudine-resistant isolate as well as a multidrug-resistant isolate, the combination of saquinavir and indinavir demonstrated antagonism at all doses.
- IT 127779-20-8, Saquinavir  
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(antagonism between HIV-1 protease inhibitors indinavir and saquinavir in vitro)
- L9 ANSWER 14 OF 82 CAPLUS COPYRIGHT 1999 ACS
- AN 1997:337741 CAPLUS
- DN 127:12782
- TI Human immunodeficiency virus type 1 protease inhibitors
- AU Mcdonald, Cheryl K.; Kuritzkes, Daniel R.
- CS Division of Infectious Diseases, University of Colorado Health Sciences Center, Denver, USA
- SO Arch. Intern. Med. (1997), 157(9), 951-959  
CODEN: AIMDAP; ISSN: 0003-9926
- PB American Medical Association
- DT Journal; General Review
- LA English
- AB A review with 86 refs. Until recently, treatment for human immunodeficiency virus type 1 (HIV-1) infection was limited to the use of nucleoside inhibitors of the viral enzyme reverse transcriptase. While these agents initially offered promise, they have only modest antiviral activity and the benefits of treatment are limited by the emergence of drug resistance and dose-limiting toxic effects.1,2 Development of more potent drugs that target
- Searcher : Shears 308-4994

different stages of the virus life cycle has thus been aggressively pursued. Efforts to develop inhibitors of HIV-1 protease have yielded a potent new class of compds. that suppress HIV-1 replication to an extent far greater than was previously attainable. Four protease inhibitors, saquinavir mesylate, ritonavir, nelfinavir, and indinavir sulfate, have been approved by the Food and Drug Administration. Other agents are undergoing active investigation. The purpose of this article is to review the currently available data on those agents that have been approved for clin. use.

IT 149845-06-7, Saquinavir mesylate 155213-67-5,  
Ritonavir

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(HIV-1 protease inhibitors design  
and antiviral activity)

L9 ANSWER 15 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1997:283408 CAPLUS

DN 127:12922

TI Metabolism and disposition of the HIV-1 protease inhibitor ritonavir (ABT-538) in rats, dogs, and humans

AU Denissen, Jon F.; Grabowski, Brian A.; Johnson, Marianne K.; Buko, Alex M.; Kempf, Dale J.; Thomas, Samuel B.; Surber, Bruce W.

CS Abbott Lab., Abbott Park, IL, 60064, USA

SO Drug Metab. Dispos. (1997), 25(4), 489-501

CODEN: DMDSAI; ISSN: 0090-9556

PB Williams & Wilkins

DT Journal

LA English

AB The metab. and disposition of [<sup>14</sup>C]ritonavir (ABT-538, NOR-VIR), a potent, orally active HIV-1 protease inhibitor, were investigated in male and female Sprague-Dawley rats, beagle dogs, and HIV-neg. male human volunteers. Rats and dogs received a 5 mg/kg i.v., 20 mg/kg oral or 20 mg/kg intraduodenal dose, whereas humans received a single 600-mg liq. oral dose. Ritonavir was cleared primarily via hepatobiliary elimination in all three species. After i.v. or oral dosing in either rats or dogs, >92% of the dose was recovered in rat and dog feces and .ltoreq.4% was recovered in the urine. Humans excreted 86.3% of the oral dose in feces and 11.3% in urine over 6 days. Bile-exteriorized rats and dogs excreted 85.5% and 39.8%, resp., of the i.v. dose in bile, with <3% recovered in urine. Radio-HPLC anal. of bile, feces, and urine from all three species indicated extensive metab. of ritonavir to a no. of oxidative metabolites, some being species-specific, and all involving metab. at the terminal functional groups of the mol. Glucuronide metabolites were obsd. in dog only. Plasma radioactivity consisted predominantly of unchanged parent drug in all three species. M-2,

Searcher : Shears 308-4994

the product of hydroxylation at the methine carbon of the terminal iso-Pr moiety of ritonavir, was the only metabolite present in human plasma and made up 30.4% of the total dose recovered in human excreta over 6 days. Tissue distribution of ritonavir in rat was widespread, with good distribution into lymphatic tissue but low CNS penetration. Plasma protein binding of ritonavir was high (96-99.5%) in all species and was nonsaturable in humans at concns. up to 30 .mu.g/mL. Partitioning into the formed elements of whole blood was minimal.

IT 155213-67-5, Ritonavir

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)

(HIV-1 protease inhibitor ritonavir

(ABT-538) metab. and disposition in rats, dogs, and humans)

IT 176655-56-4 190649-39-9

RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)

(HIV-1 protease inhibitor ritonavir

(ABT-538) metab. and disposition in rats, dogs, and humans)

IT 176655-55-3 176655-57-5 190649-37-7

190649-38-8 190649-40-2

RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)

(HIV-1 protease inhibitor ritonavir

(ABT-538) metab. and disposition in rats, dogs, and humans)

L9 ANSWER 16 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1997:219835 CAPLUS

DN 126:301429

TI Lack of stereospecificity in the binding of the P2 amino acid of ritonavir to HIV protease

AU Kempf, Dale J.; Molla, Akhteruzzaman; Marsh, Kennan C.; Park, Chang; Rodrigues, A. David; Komeyeva, Marina; Vasavanonda, Sudthida; McDonald, Edith; Flentge, Charles A.; et al.

CS Abbott Laboratories, D-47D, AP9A, Abbott Park, IL, 60064, USA

SO Bioorg. Med. Chem. Lett. (1997), 7(6), 699-704

CODEN: BMCLE8; ISSN: 0960-894X

PB Elsevier

DT Journal

LA English

AB The biol. and pharmacokinetic properties of the HIV protease inhibitor ritonavir and its D-valinyl diastereomer, A-117673, were found to be indistinguishable. The X-ray crystal structure of the A-117673/HIV protease complex demonstrated similar binding modes for the two inhibitors, with a ca 1 .ANG. difference in the backbone that allows the valine side chain of both compds. to project into the S2 subsite of the enzyme.

IT 155213-67-5, Ritonavir 183388-65-0, A 117673

RL: BAC (Biological activity or effector, except adverse); THU

Searcher : Shears 308-4994

(Therapeutic use); BIOL (Biological study); USES (Uses)  
 (HIV protease inhibitor ritonavir  
 and diastereomer antiviral and pharmacokinetic properties)

L9 ANSWER 17 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1997:208119 CAPLUS  
 DN 126:293367  
 TI Substituted cyclic carbonyls and derivatives thereof useful as  
 retroviral protease inhibitors  
 IN Lam, Patrick Y.; Jadhav, Prabhakar K.; Eyermann, Charles J.; Hodge,  
 Carl N.; De Lucca, George V.; Rodgers, James D.  
 PA The Du Pont Merck Pharmaceutical Company, USA  
 SO U.S., 198 pp. Cont.-in-part of U.S. Ser. No. 47,330, abandoned.  
 CODEN: USXXAM  
 DT Patent  
 LA English  
 FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5610294	A	19970311	US 94-197630	19940216
	EP 765873	A1	19970402	EP 96-118182	19921013
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, SE				
	LV 10096	B	19950420	LV 93-341	19930514
	WO 9419329	A1	19940901	WO 94-US1609	19940223
	W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, SK				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2156594	AA	19940901	CA 94-2156594	19940223
	AU 9465493	A1	19940914	AU 94-65493	19940223
	EP 686151	A1	19951213	EP 94-913262	19940223
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 08509700	T2	19961015	JP 94-519072	19940223
	EP 858999	A1	19980819	EP 98-106311	19940223
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	ZA 9401325	A	19950825	ZA 94-1325	19940225
	US 5506355	A	19960409	US 94-269281	19940630
	US 5559252	A	19960924	US 94-268609	19940630
	AU 9532895	A1	19960523	AU 95-32895	19950926
	US 5811422	A	19980922	US 96-770546	19961122
PRAI	US 91-776491		19911011		
	US 92-883944		19920515		
	US 92-953272		19920930		
	US 93-23439		19930226		
	US 93-47330		19930415		
	EP 92-922262		19921013		
	US 94-197630		19940216		

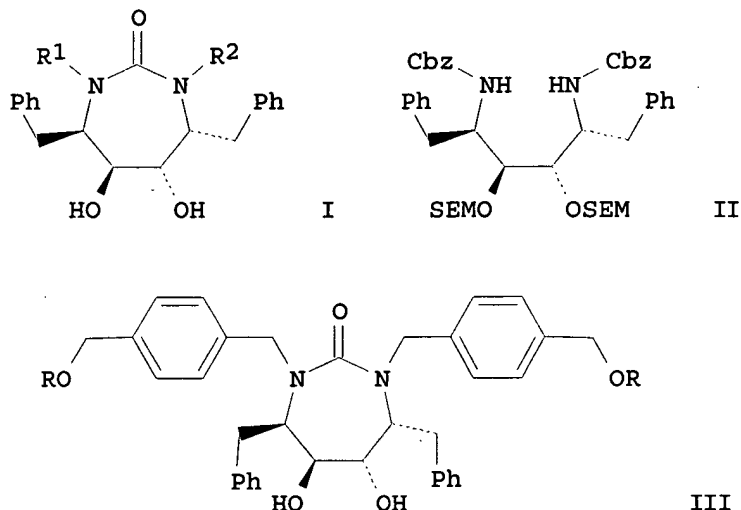
Searcher : Shears 308-4994

EP 94-913262 19940223

WO 94-US1609 19940223

OS MARPAT 126:293367

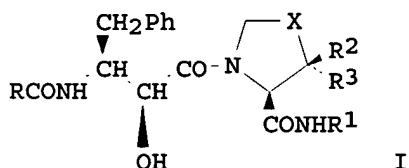
GI



AB The invention relates to substituted cyclic carbonyl compds. and derivs., and particularly to cyclic urea derivs. such as I [R1, R2 = H, alkyl, allyl, cyclopropylmethyl, (un)substituted benzyl, etc.]. The compds. are retroviral protease inhibitors, useful in pharmaceutical compns. and methods for treating viral infection. They include prodrugs which have improved aq. soly. and oral bioavailability. For instance, the protected diamine-diol II [Cbz = CO<sub>2</sub>CH<sub>2</sub>Ph, SEM = CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>] was N-deprotected by hydrogenolysis (99%), then cyclized with carbonyldiimidazole in CH<sub>2</sub>Cl<sub>2</sub> (93%) to give a cyclic urea intermediate. N,N'-Dialkylation of this using NaH in DMF and alkyl bromides, followed by acid hydrolysis using HCl in MeOH-dioxane gave a variety of I, e.g., compd. III [R = H] (IV). Protection of IV as the acetonide (90%) and esterification with excess N,N-dimethylglycine using EDCI (73%) gave the prodrug III.2HCl [R = COCH<sub>2</sub>NMe<sub>2</sub>] (V). In the HIV-1 protease transgenic mouse model, as measured by delay of cataract onset, IV gave a delay of 5 days past control at 100 mg/kg i.p. bid, and 45 days at 400 mg/kg i.p. bid. However, solid IV had only low oral bioavailability, and still only 5% at 40 mg/kg when administered in glycol excipient. In contrast, the prodrug V gave 12% mean bioavailability of IV at only 8 mg/kg orally without excipient.

L9 ANSWER 18 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1997:132760 CAPLUS  
 DN 126:144550  
 TI HIV-protease inhibitors  
 IN Kato, Ryohei; Mimoto, Tsutomu; Fukazawa, Tominaga; Morohashi, Naoko;  
 Kiso, Yoshiaki  
 PA Japan Energy Corporation, Japan  
 SO Eur. Pat. Appl., 34 pp.  
 CODEN: EPXXDW  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 751145	A2	19970102	EP 96-304764	19960628
	EP 751145	A3	19971008		
	R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IT, LI, LU, NL, SE				
	CA 2179935	AA	19961231	CA 96-2179935	19960626
	JP 10025242	A2	19980127	JP 96-185631	19960626
	NO 9602748	A	19970102	NO 96-2748	19960628
	AU 9656285	A1	19970206	AU 96-56285	19960628
PRAI	JP 95-188151		19950630		
	JP 96-140678		19960510		
OS	MARPAT 126:144550				
GI					



AB Dipeptides I (X = CH<sub>2</sub>, CHCl, O, S, SO<sub>2</sub>; R = 5- or 6-membered monocyclic hydrocarbon or heterocyclic group; R<sub>1</sub> = alkyl, monocyclic hydrocarbon group; R<sub>2</sub>, R<sub>3</sub> = H, alkyl) were prep'd. as HIV-protease inhibitors. Thus, treatment of a suspension of (R)-[(2S,3S)-3-amino-2-hydroxy-4-phenylbutanoyl]-1,3-thiazolidine-4-N'-tert-butylcarboxamide, (2S,3S)-H-AHPBA-Thz-NH-tBu, and benzoic acid in DMF with EDC.HCl and HOBt-H<sub>2</sub>O for 14 h at room temp. afforded benzoyl deriv. I (X = S, R = Ph, R<sub>1</sub> = t-Bu, R<sub>2</sub> = R<sub>3</sub> = H). The latter comp'd. showed 52.0 % HIV protease inhibitor activity at a concn. of 5 .mu.M.  
 IT 183107-57-5P 183107-74-6P 186537-87-1P  
 186538-03-4P

Searcher : Shears 308-4994

RL: BAC (Biological activity or effector, except adverse); SPN  
(Synthetic preparation); THU (Therapeutic use); BIOL (Biological  
study); PREP (Preparation); USES (Uses)  
(prepn. of HIV-protease inhibitors)

IT 153380-43-9 177355-09-8

RL: RCT (Reactant)  
(prepn. of HIV-protease inhibitors)

L9 ANSWER 19 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1996:693956 CAPLUS

DN 126:139294

TI HIV-Protease inhibitors. A new class of substances in antiretroviral  
therapy

AU Mauss, S.; Seidlitz, B.; Jablonowski, H.; Haeussinger, D.

CS Klinik Gastroenterologie Hepatologie Infektiologie, Univ.  
Duesseldorf, Duesseldorf, D-40225, Germany

SO Dtsch. Med. Wochenschr. (1996), 121(44), 1369-1374

CODEN: DMWOAX; ISSN: 0012-0472

PB Thieme

DT Journal; General Review

LA German

AB A review with 33 refs. on the HIV-protease inhibitors saquinavir,  
ritonavir, and indinavir.

IT 127779-20-8, Saquinavir 155213-67-5, Ritonavir

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(HIV protease inhibitors in  
antiretroviral therapy)

L9 ANSWER 20 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1996:657059 CAPLUS

DN 125:329477

TI Process for the preparation of HIV protease inhibiting peptide  
analogs.

IN Tien, Jien-heh J.; Menzia, Jerome A.; Cooper, Arthur J.

PA Abbott Laboratories, USA

SO U.S., 7 pp.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5567823	A	19961022	US 95-469965	19950606
	WO 9639398	A1	19961212	WO 96-US6812	19960513
	W: CA, JP, MX				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,				
	PT, SE				
	CA 2219983	AA	19961212	CA 96-2219983	19960513
	EP 830353	A1	19980325	EP 96-915755	19960513

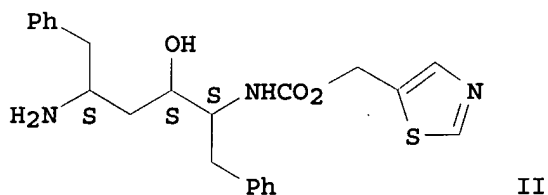
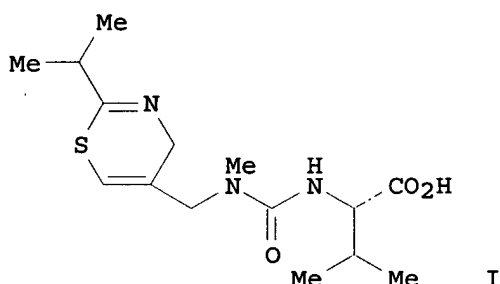
Searcher : Shears 308-4994

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT,  
IE, FI

PRAI US 95-469965 19950606

WO 96-US6812 19960513

GI



AB (2S,3S,5S)-5-[N-[N-[N-methyl-N-[(2-isopropyl-4-thiazolyl)methyl]amino]carbonyl]-(D- and L-)valinyl]amino]-2-[N-[(5-thiazolyl)methoxycarbonyl]amino]-1,6-diphenyl-3-hydroxyhexane were prepd. without isolation of intermediates by (I) conversion of D- or L-I to a mixed anhydride, (2) conversion of the mixed anhydride to an active ester, and (3) coupling of the active ester with amine (II).

IT 155213-67-5P 183388-65-0P

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(prepn. of HIV protease inhibiting  
peptide analogs)

IT 183388-64-9

RL: RCT (Reactant)

(prepn. of HIV protease inhibiting  
peptide analogs)

IT 144164-11-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)

(prepn. of HIV protease inhibiting  
peptide analogs)



L9 ANSWER 21 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1996:452798 CAPLUS  
 DN 125:168034  
 TI Method for preparing HIV-protease-inhibiting N-monosubstituted and  
 N,N'-disubstituted unsymmetrical cyclic ureas via alkylation and  
 dealkylation of intermediate isoureas  
 IN Rodgers, James D.; Sun, Jung Hui  
 PA Dupont Merck Pharmaceutical Co., USA  
 SO U.S., 33 pp.  
 CODEN: USXXAM  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5532357	A	19960702	US 95-481683	19950607
	WO 9640652	A1	19961219	WO 96-US9021	19960606
	W: AM, AT, AU, AZ, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, HU, IL, JP, KG, KR, KZ, LT, LU, LV, MD, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, UA, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2223391	AA	19961219	CA 96-2223391	19960606
	AU 9659868	A1	19961230	AU 96-59868	19960606
	EP 837855	A1	19980429	EP 96-917212	19960606
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	LT 4381	B	19980427	LT 97-188	19971203
	NO 9705679	A	19980202	NO 97-5679	19971205
	LV 12045	B	19980920	LV 97-248	19980128
PRAI	US 95-481683		19950607		
	WO 96-US9021		19960606		
OS	CASREACT 125:168034; MARPAT 125:168034				
GI					

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB A process is claimed for prepn. of title compds. I or  
 pharmaceutically acceptable salts or prodrug forms thereof, wherein:  
 R4 and R7 are the same and are selected from the following groups:  
 C1-C8 alkyl substituted with 0-3 R11; C2-C8 alkenyl substituted with  
 0-3 R11; C2-C8 alkynyl substituted with 0-3 R11; R11 is  
 independently selected at each occurrence from the group consisting  
 of, e.g., H, keto, halogen, cyano, Ph, benzyl; R22 and R23 are  
 independently selected at each occurrence from the group consisting  
 Searcher : Shears 308-4994

of, e.g., C1-C8 alkyl substituted with 0-3 R31; C2-C8 alkenyl substituted with 0-3 R31; C2-C8 alkynyl substituted with 0-3 R31; R31 is independently selected at each occurrence from, e.g., OH, C1-C4 alkoxy, keto, halo, cyano, benzyl; and all functional groups that are reactive with the chem. of this process are protected in such a form that the protecting groups may be kept or removed. This process comprises the steps of (1) contacting isourea II wherein: R1 is Me or Et; R5 and R6 are the same and are selected from, e.g., C1-C6 alkyl substituted with 0-3 R11; C3-C6 alkoxyalkyl substituted with 0-3 R11; C1-C6 alkylcarbonyl substituted with 0-3 R11; R5 and R6 may also be taken together along with the oxygen atoms to which they are attached to form a cyclic acetal group, in an aprotic solvent with at least one molar equivalent of a nitrogen alkylating agent R23-Z, wherein Z is leaving group such as halide or sulfonate and R23 is as defined above, for a period of time sufficient to form cyclic urea III which is optionally isolated; and step (2) contacting III with a reagent or condition or combination of reagents and/or conditions for a period of time sufficient to effect the removal of R5, R6 and any protecting groups and/or to convert functional groups to their desired form to form I which is isolated. Alternatively, monoalkylated isourea II is dealkylated and deprotected to provide monosubstituted urea IV. Thus, e.g., methylation of cyclic urea V with Me triflate afforded isourea VI (75%); alkylation of VI with 3-cyano-4-fluorobenzyl bromide (NaH/DMF) afforded monosubstituted isourea VII (92%); benzylation of VII with PhCH<sub>2</sub>Br in MeCN afforded disubstituted urea VIII (95%); heterocyclization of VIII with hydrazine afforded the corresponding R23 = 3-aminoindazol-5-ylmethyl acetamide deriv. (100%) which was subsequently deprotected in HCl/THF to provide the diol.

IT 153223-10-0

RL: RCT (Reactant)

(method for prepg. **HIV-protease-****inhibiting** N-monosubstituted and N,N'-disubstituted

unsym. cyclic ureas via alkylation of intermediate isoureas)

L9 ANSWER 22 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1996:357017 CAPLUS

DN 125:26233

TI HIV protease inhibitor combination, and therapeutic use

IN Deutsch, Paul J.; Emini, Emilio A.; Vacca, Joseph P.

PA Merck and Co., Inc., USA

SO PCT Int. Appl., 29 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	---	-----	-----	-----
PI	WO 9604913	A1	19960222	WO 95-US9956	19950807
			Searcher	: Shears	308-4994

W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP,  
 KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO,  
 RU, SG, SI, SK, TJ, TM, TT, UA, UZ

RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE,  
 IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML,  
 MR, NE, SN, TD, TG

CA 2197207 AA 19960222 CA 95-2197207 19950807

AU 9533611 A1 19960307 AU 95-33611 19950807

AU 698664 B2 19981105

EP 774969 A1 19970528 EP 95-930118 19950807

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT,  
 SE

CN 1160350 A 19970924 CN 95-195548 19950807

HU 76540 A2 19970929 HU 97-402 19950807

JP 10504036 T2 19980414 JP 95-507422 19950807

ZA 9506662 A 19960325 ZA 95-6662 19950810

FI 9700565 A 19970210 FI 97-565 19970210

NO 9700632 A 19970410 NO 97-632 19970211

PRAI US 94-289474 19940811

US 94-339369 19941114

US 95-492461 19950720

WO 95-US9956 19950807

AB The combination of the HIV protease inhibitor N-[2(R)-hydroxy-1(S)-indanyl]-2(R)phenylmethyl-4(S)-hydroxy-5-[1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarbamoyl)piperazinyl)]pentaneamide and any one or more of four other potent HIV protease inhibitors is useful in the inhibition of HIV protease, the prevention or treatment of infection by HIV and the treatment of AIDS, either as compds., pharmaceutically acceptable salts, pharmaceutical compn. ingredients, whether or not in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of treating AIDS and methods of preventing or treating infection by HIV are also described.

IT 127779-20-8 155213-67-5

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(HIV protease inhibitor  
 combination, and therapeutic use)

L9 ANSWER 23 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1996:228484 CAPLUS

DN 124:290277

TI HIV protease inhibitor combinations.

IN Barrish, Joel C.; Colonna, Richard J.; Lin, Pin-Fang M.

PA Bristol-Myers Squibb Co., USA

SO Eur. Pat. Appl., 29 pp.

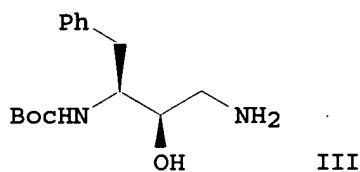
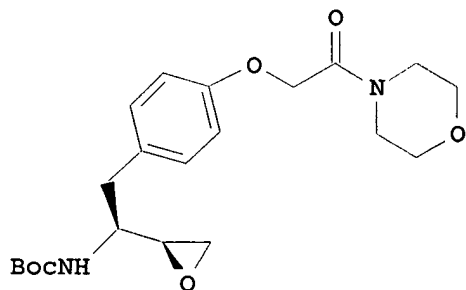
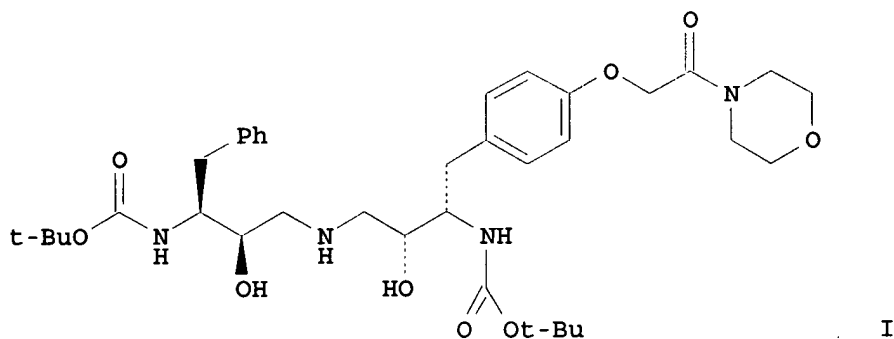
CODEN: EPXXDW

DT Patent

LA English

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	----	-----	-----	-----
PI	EP 691345	A2	19960110	EP 95-304718	19950705
	EP 691345	A3	19960228		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	US 1649	H1	19970506	US 95-436868	19950517
	AU 9524800	A1	19960118	AU 95-24800	19950704
PRAI	US 94-270614		19940705		
	US 95-436868		19950517		
	US 87-79978		19870731		
GI					



AB A product comprising HIV-1 protease inhibitor (I) (BMS-186318) and .gtoreq.1 of RO 31-8959, SC-52151, A-77003, A-80987, ABT-538, L-735,524, and AG-1343 is claimed. The combinations may eliminate or substantially reduce viral cross-resistance seen with use of individual HIV-1 protease inhibitors. A synthesis of I via coupling of epoxide (II) with aminoalc. (III) is given.

IT 127779-20-8, RO 31-8959 134878-17-4, A-77003  
144141-97-9, A 80987 155213-67-5, ABT-538

RL: BAC (Biological activity or effector, except adverse); THU  
Searcher : Shears 308-4994

(Therapeutic use); BIOL (Biological study); USES (Uses)  
 (HIV protease inhibitor  
 combinations)

L9 ANSWER 24 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1996:222223 CAPLUS  
 DN 125:25473  
 TI Saquinavir. A new drug against HIV  
 AU Strohmaier, Birgit  
 CS Passau, Germany  
 SO Pharm. Ztg. (1996), 141(14), 45-6  
 CODEN: PHZIAP; ISSN: 0031-7136  
 DT Journal; General Review  
 LA German  
 AB A review without refs., describing the structure, resistance  
 development, and pharmacokinetics of the protease inhibitor  
 saquinavir (I), and combination treatment of HIV-infected patients  
 with zidovudine, zalcitabine, and I.  
 IT 127779-20-8, Saquinavir  
 RL: BAC (Biological activity or effector, except adverse); THU  
 (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (saquinavir as HIV-protease inhibitor  
 )

L9 ANSWER 25 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1996:148284 CAPLUS  
 DN 124:219422  
 TI A Possible Involvement of Solvent-Induced Interactions in Drug  
 Design  
 AU Wang, Hongwu; Ben-Naim, Arie  
 CS Department of Physical Chemistry, Hebrew University of Jerusalem,  
 Jerusalem, 91904, Israel  
 SO J. Med. Chem. (1996), 39(7), 1531-9  
 CODEN: JMCMAR; ISSN: 0022-2623  
 DT Journal  
 LA English  
 OS CJACS  
 AB We propose to study a new factor in designing new drugs. Most  
 approaches to the drug design problem focus on the direct  
 interactions between the drug and the corresponding target. We  
 propose to study specific solvent-induced effects that can  
 contribute to the binding Gibbs energy between the drug and its  
 target. We est. that these indirect effects will contribute  
 significantly to the binding affinity and hopefully improve the  
 clin. efficiency of the drugs.  
 IT 144141-70-8, A78791  
 RL: BPR (Biological process); BIOL (Biological study); PROC  
 (Process)  
 (HIV-1 protease inhibitor;

Searcher : Shears 308-4994

involvement of solvent-induced interactions in drug design)

L9 ANSWER 26 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1996:129437 CAPLUS

DN 124:219526

TI Resistance of human immunodeficiency virus type 1 to protease inhibitors: selection of resistance mutations in the presence and absence of the drug

AU Borman, Andrew M.; Paulous, Sylvie; Clavel, Francois

CS Unite d'Oncologie Virale CNRS URA 1157, Inst. Pasteur, Paris, 75724, Fr.

SO J. Gen. Virol. (1996), 77(3), 419-26

CODEN: JGVIAY; ISSN: 0022-1317

DT Journal

LA English

AB Inhibitors of the human immunodeficiency virus (HIV) protease are a promising class of antiviral agents that dramatically reduce HIV replication both in culture and in infected patients. However, as for many other antiviral compds., long-term efficacy of these agents is impeded by the emergence of virus variants with increased resistance to their inhibitory action, following selection of specific mutations in the protease coding sequence. We have studied HIV-1 variants that emerged at different stages of selection in the presence of the C2-sym. protease inhibitor ABT-77003. The selection of variants was a gradual process during which mutations accumulated at different sites in the protease, generating virus populations with increasing levels of resistance to the drug. The initially selected viruses had a low level of resistance as well as a markedly reduced replicative capacity. Further accumulation of mutations at secondary sites led to an improvement in both drug resistance and replication. In spite of their reduced infectivity, partially selected virus populations did not readily revert to wild-type when serially passaged in drug-free conditions. Instead, even in the absence of drug, secondary mutations identical to those selected in the presence of the inhibitor continued to emerge. These mutations improved both the intrinsic replicative capacity of the virus and its level of resistance to the inhibitor, suggesting that once committed to drug resistance, readaptation and the enzyme to its natural substrate leads to a redn. of its sensitivity to the inhibitor.

IT 134878-17-4, A77003

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(resistance of HIV1 to protease

inhibitor ABT-77003 and selection of resistance mutations in the presence and absence of the drug)

L9 ANSWER 27 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1996:98265 CAPLUS

Searcher : Shears 308-4994

DN 124:169196  
TI The binding energy of HIV-1 protease inhibitor  
AU Ka, Jaejin; Park, Sang-Hyun; Kim, Hojing  
CS Department of Chemistry, Seoul National University, Seoul, 151-742,  
S. Korea  
SO Bull. Korean Chem. Soc. (1996), 17(1), 19-24  
CODEN: BKCSDE; ISSN: 0253-2964  
DT Journal  
LA English  
AB The potential energies of HIV-1 protease, inhibitor, and their  
complex have been calcd. by mol. mechanics and the "binding energy",  
defined as the difference between the potential energy of complex  
and the sum of potential energies of HIV-1 protease and its  
inhibitor, has been compared to the free energy in inhibition  
reaction. The trend in these binding energies seems to agree with  
that in free energies.  
IT 132748-20-0, JG365  
RL: PRP (Properties)  
(HIV-1 proteinase inhibitor;  
binding energies of HIV-1 protease and synthetic  
peptide inhibitors)

L9 ANSWER 28 OF 82 CAPLUS COPYRIGHT 1999 ACS  
AN 1996:26723 CAPLUS  
DN 124:202216  
TI Stereoselective Synthesis of HIV-1 Protease Inhibitor DMP 323  
AU Pierce, Michael E.; Harris, Gregory D.; Islam, Qamrul; Radesca,  
Lilian A.; Storace, Louis; Waltermire, Robert E.; Wat, Ed; Jadhav,  
Prabhakar K.; Emmett, George C.  
CS Chemical Proces R and D Department, DuPont Merck Pharmaceutical  
Company, Deepwater, NJ, 08023-0999, USA  
SO J. Org. Chem. (1996), 61(2), 444-50  
CODEN: JOCEAH; ISSN: 0022-3263  
DT Journal  
LA English  
OS CJACS  
AB DMP 323, a potent HIV-1 protease inhibitor, has been synthesized by  
an efficient stereoselective process, amenable to large scale  
preps. The core C2 sym. diol was synthesized by a stereoselective  
pinacol coupling of CBZ protected D-phenylalanine. Judicious  
selection of protecting groups allowed cyclic urea formation under  
mild conditions, enhanced the ease of bis-alkylation, and led to  
intermediates which were easily purified without chromatog. Addnl.,  
a one-pot, high yield process was developed to prep. the alkylating  
agent, 4-[(triphenylmethoxy)methyl]benzyl chloride from  
1,4-benzenedimethanol.  
IT 153223-10-0P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)  
(stereoselective synthesis of HIV-1 protease  
Searcher : Shears 308-4994

## inhibitor DMP 323)

L9 ANSWER 29 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1995:994185 CAPLUS  
 DN 124:87033  
 TI Preparation of HIV protease inhibitors and their  
 (aminohydroxyalkyl)piperazine intermediates.  
 IN Jungheim, Louis Nickolaus; Shepherd, Timothy Alan  
 PA Lilly, Eli, and Co., USA  
 SO PCT Int. Appl., 133 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9521164	A1	19950810	WO 94-US11352	19941006
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN				
	RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5461154	A	19951024	US 94-190630	19940202
	CA 2180860	AA	19950810	CA 94-2180860	19941006
	AU 9479304	A1	19950821	AU 94-79304	19941006
	EP 741719	A1	19961113	EP 94-930064	19941006
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	HU 76285	A2	19970728	HU 96-2105	19941006
	BR 9408530	A	19970805	BR 94-8530	19941006
	JP 09509657	T2	19970930	JP 94-520584	19941006
PRAI	US 94-190630		19940202		
	WO 94-US11352		19941006		
OS	MARPAT 124:87033				
GI	For diagram(s), see printed CA Issue.				
AB	Intermediates [I; R = alkyl, pyridylmethyl; R1 = aryl, arylthio; R3 = CON(R4)2, Q1, Q2; p = 4, 5; R4 = H, alkyl, hydroxyalkyl; R5, R6 = H, OH, alkyl, alkoxy, hydroxyalkyl], were prep'd. by (a) redn. of pyrazines (II) to give piperazines, (b) alkylation of the piperazines to give intermediates (III), (c) alkylation of III with (IV; R11 = protecting group), and (d) optional deprotection. Thus, pyrazine-2-carboxylic acid in DMF/THF was treated with carbonyldiimidazole and then with Me3CNH2 to give 95% pyrazine 2-N-tert-butylcarboxamide. The latter in EtOH was hydrogenated at 60 psi and 40.degree. overnight to give 95% piperazine 2-N-tert-butylcarboxamide. This in H2O/MeCN was treated with K2CO3 and 3-chloromethylpyridine hydrochloride overnight to give 18%				

Searcher : Shears 308-4994



4-(pyrid-3-ylmethyl)piperazine 2-N-tert-butylcarboxamide. Reflux of the latter compd. with [1S-(1R\*,1'R\*)]-1-[(1'-N-benzyloxycarbonylamino-2'-phenyl)ethyl]oxirane in Me<sub>2</sub>CHOH gave 26% [2S-(2R\*,2S\*,3'R\*)]-1-[2'-hydroxy-3'-(N-benzyloxycarbonylamino)-4'-phenylbutyl]-4-(pyrid-3''-ylmethyl)piperazine 2-N-tert-butylcarboxamide. [3S-(3R\*,8aR\*,2'S\*,3'S\*)]-2-[2'-hydroxy-3'-phenylthiomethyl-4'-aza-5'-(2''-methyl-3''-hydroxyphenyl)pentyl]decahydroisoquinoline 3-N-tert-butylcarboxamide (prepn. given) inhibited HIV-1 protease with a normalized IC<sub>50</sub> = 0.25 ng/mL.

IT 168898-46-2P 168898-47-3P 168898-48-4P  
168898-49-5P 168898-50-8P 168898-52-0P  
168898-53-1P 168898-54-2P 168898-55-3P  
168898-56-4P 168898-57-5P 168898-58-6P  
168898-59-7P 168898-60-0P 168898-61-1P  
168898-62-2P 168898-63-3P 168898-65-5P  
168898-66-6P 168898-67-7P 168898-78-0P  
168898-79-1P 169104-88-5P 169104-89-6P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of HIV protease inhibitors  
and their (aminohydroxyalkyl)piperazine intermediates)

IT 128018-20-2P 128053-39-4P 136522-17-3P  
137431-05-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of HIV protease inhibitors  
and their (aminohydroxyalkyl)piperazine intermediates)

L9 ANSWER 30 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1995:994162 CAPLUS

DN 124:87790

TI Pharmaceutical compositions containing HIV protease inhibitors and their preparation.

IN Al-Razzak, Laman; Marsh, Kennan C.; Manning, Lourdes P.; Kaul, Dilip

PA Abbott Laboratories, USA

SO PCT Int. Appl., 58 pp.

CODEN: PIXXD2

DT Patent

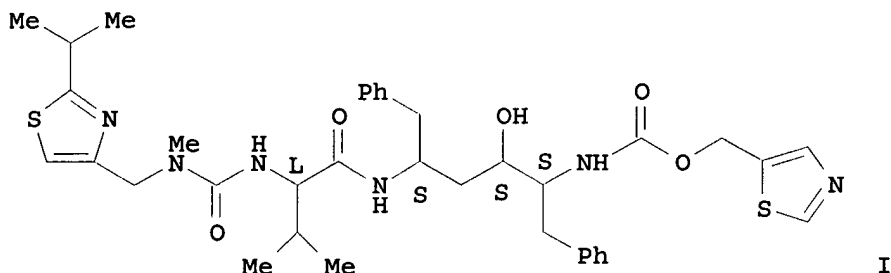
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	---	-----	-----	-----
PI	WO 9520384	A1	19950803	WO 95-US232	19950103
	W: AU, CA, JP, KR, MX				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2178632	AA	19950803	CA 95-2178632	19950103
	AU 9515248	A1	19950815	AU 95-15248	19950103
	Searcher : Shears 308-4994				

EP 732923	A1	19960925	EP 95-906790	19950103
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 09508383	T2	19970826	JP 95-520059	19950103
US 5484801	A	19960116	US 95-440277	19950512
PRAI US 94-189021		19940128		
US 94-283239		19940729		
WO 95-US232		19950103		

GI



AB A pharmaceutical compn. which comprises a soln. of an HIV protease inhibiting compd. (e.g., I) in a pharmaceutically acceptable org. solvent comprising a mixt. of (1): (a) a solvent selected from propylene glycol and polyethylene glycol or (b) a solvent selected from polyoxyethyleneglycerol triricinoleate, polyethylene glycol 40 hydrogenated castor oil, fractioned coconut oil, polyoxyethylene 20 sorbitan monooleate and 2-(2-ethoxyethoxy)ethanol or (c) a mixt. thereof; and (2) ethanol or propylene glycol, is claimed. I was prepd. in many steps and its bioavailability in various formulations was studied.

IT 155213-67-5P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(pharmaceutical compns. contg. HIV protease inhibitors and their prepn.)

IT 143838-10-2P 144164-10-3P

RL: BYP (Byproduct); PREP (Preparation)

(pharmaceutical compns. contg. HIV protease inhibitors and their prepn.)

IT 156732-15-9

RL: RCT (Reactant)

(pharmaceutical compns. contg. HIV protease inhibitors and their prepn.)

IT 137649-69-5P 144141-68-4P 144163-44-0P

144163-85-9P 144164-11-4P 162849-93-6P

Searcher : Shears 308-4994

162849-95-8P 162990-03-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)  
 (pharmaceutical compns. contg. **HIV protease inhibitors** and their prepn.)

IT 162990-01-4

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (pharmaceutical compns. contg. **HIV protease inhibitors** and their prepn.)

L9 ANSWER 31 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1995:938815 CAPLUS

DN 124:105570

TI Selectivity in the Inhibition of HIV and FIV Protease: Inhibitory  
 and Mechanistic Studies of Pyrrolidine-Containing .alpha.-Keto Amide  
 and Hydroxyethylamine Core Structures

AU Slee, Deborah H.; Laslo, Karen L.; Elder, John H.; Ollmann, Ian R.;  
 Gustchina, Alla; Kervinen, Jukka; Zdanov, Alexander; Wlodawer,  
 Alexander; Wong, Chi-Huey

CS Scripps Research Institute, La Jolla, CA, 92037, USA

SO J. Am. Chem. Soc. (1995), 117(48), 11867-78

CODEN: JACSAT; ISSN: 0002-7863

DT Journal

LA English

OS CJACS

AB This study describes the development of new pyrrolidine-contg.  
 .alpha.-keto amide and hydroxyethylamine core structures as  
 mechanism based inhibitors of the HIV and FIV proteases. The  
 .alpha.-keto amide core structure is approx. 300-fold better than  
 the corresponding hydroxyethylamine isosteric structure and  
 1300-fold better than the corresponding phosphinic acid deriv. as an  
 inhibitor of the HIV protease. The .alpha.-keto amide is however  
 not hydrated until it is bound to the HIV protease as indicated by  
 the NMR study and the x-ray structural anal. Further anal. of the  
 inhibition activities of hydroxyethylamine isosteres contg. modified  
 pyrrolidine derivs. revealed that a cis-methoxy group at C-4 of the  
 pyrrolidine would improve the binding 5- and 25-fold for the  
 trans-isomer. Of the core structures prepd. as inhibitors of the  
 HIV protease, none show significant inhibitory activity against the  
 mechanistically identical FIV protease, and addnl. complementary  
 groups are needed to improve inhibition.

IT 141197-75-3P

RL: BAC (Biological activity or effector, except adverse); PRP  
 (Properties); SPN (Synthetic preparation); THU (Therapeutic use);  
 BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (**HIV and FIV proteases**  
**inhibition** by pyrrolidine-contg. .alpha.-keto amide and  
 hydroxyethylamines)

IT 128018-20-2P 172696-14-9P 172696-18-3P

172823-16-4P 172823-17-5P 172883-15-7P

Searcher : Shears 308-4994

172953-21-8P

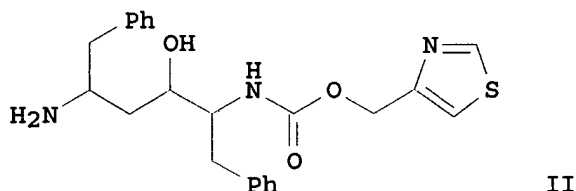
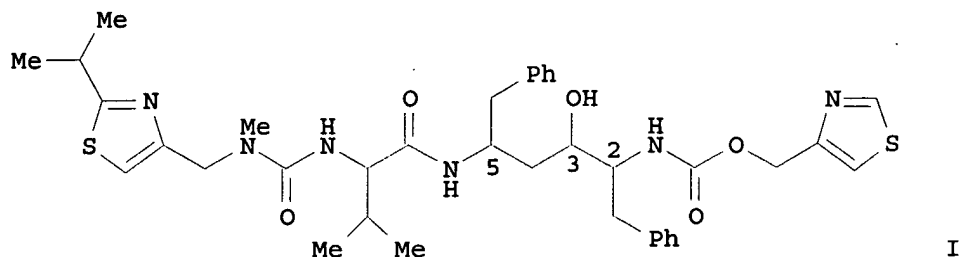
RL: BAC (Biological activity or effector, except adverse); SPN  
(Synthetic preparation); THU (Therapeutic use); BIOL (Biological  
study); PREP (Preparation); USES (Uses)

(HIV and FIV proteases

inhibition by pyrrolidine-contg. .alpha.-keto amide and  
hydroxyethylamines)

L9 ANSWER 32 OF 82 CAPLUS COPYRIGHT 1999 ACS  
AN 1995:887807 CAPLUS  
DN 123:314522  
TI Pharmaceutical composition for HIV protease inhibitor [ritonavir]  
with improved oral bioavailability  
IN Al-razzak, Laman A.; Marsh, Kennan C.; Pyter, Richard A.  
PA Abbott Laboratories, USA  
SO PCT Int. Appl., 55 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9509614	A1	19950413	WO 94-US10096	19940909
	W: AU, CA, JP, KR				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5559158	A	19960924	US 94-297004	19940831
	AU 9477229	A1	19950501	AU 94-77229	19940909
	AU 685509	B2	19980122		
	EP 721330	A1	19960717	EP 94-928043	19940909
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	JP 09503501	T2	19970408	JP 94-510810	19940909
PRAI	US 93-130409		19931001		
	US 94-267273		19940628		
	US 94-297004		19940831		
	WO 94-US10096		19940909		
OS	MARPAT 123:314522				
GI					



AB A solid pharmaceutical compn. is disclosed which comprises a pharmaceutically acceptable adsorbent or mixt. of adsorbents, to which is adsorbed a mixt. of: (1) a pharmaceutically acceptable org. solvent or mixt. of solvents; (2) an HIV protease-inhibiting compd.; and (3) one or more pharmaceutically acceptable acids. The solid compn. can optionally be encapsulated in a hard gelatin capsule. The compn. is particularly applicable to compd. I, and esp. its (2S,3S,5S,L)-isomer [ritonavir; II]. For example, oral administration of unformulated II to dogs gave < 2.0% mean bioavailability. In contrast, 89.6% mean bioavailability was obtained with the following capsule formulation: II 21.84, propylene glycol 10.96, ethanol 22.99, Polysorbate 80 5.31, Cremophor EL 4.4, HCl 1.18, and Cab-o-sil 26.88% by wt. Also described are addnl. oral formulations (comparative and invention), and several syntheses of II. For example, N-(benzyloxycarbonyl)-L-phenylalaninol was converted in 5 steps to (2S,3S,5S)-PhCH<sub>2</sub>CH(NHZ)CH(OH)CH<sub>2</sub>CH(NHZ)CH<sub>2</sub>Ph [Z = benzyloxycarbonyl], which was deprotected and reacted with 5-thiazolylmethyl nitrophenyl carbonate to give intermediate III and its isomer from acylation of the other amino group. Coupling of III with N-[[N-methyl-N-[(2-isopropyl-4-thiazolyl)methyl]amino]carbonyl]-L-valine [prepn. given] using the carbodiimide reagent EDC and 1-hydroxybenzotriazole gave II.

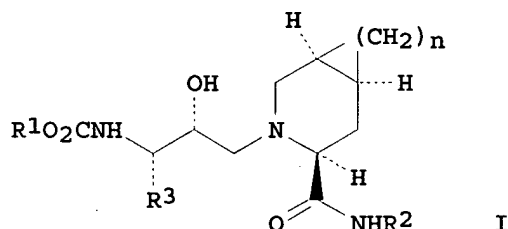
IT 155213-67-5P 162990-01-4P

RL: BPR (Biological process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(pharmaceutical compn. of HIV protease inhibitor with improved oral bioavailability)

L9 ANSWER 33 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1995:784804 CAPLUS  
 DN 123:198775  
 TI Preparation of HIV protease inhibitors  
 IN Ghosh, Arun K.; Thompson, Wayne J.; Mckee, Sean P.  
 PA Merck and Co., Inc., USA  
 SO PCT Int. Appl., 70 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9426749	A1	19941124	WO 94-US5128	19940502
	W:			AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TT, UA, UZ	
	RW:			AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG	
	AU 9468288	A1	19941212	AU 94-68288	19940502
PRAI	US 93-61897		19930514		
	WO 94-US5128		19940502		
OS	MARPAT 123:198775				
GI					



AB The title compds. [I; R1 = (un)substituted bicyclic heterocyclic ring; R2 = (un)substituted C1-5 alkyl, (un)substituted carbocyclic; R3 = (un)substituted Ph, (un)substituted cycloalkyl; n = 3, 4] [e.g., (3S,4aS,7aS,2'R,3'S,3"R,3"aS,6"aR) N-tert-Bu octahydro-2-[2'-hydroxy-4'-phenyl-3'-(3"-hexahydrofuro[2,3-b]furanyloxycarbonylamino)butyl]-1H-pyridine-3-carboxamide], useful in the inhibition of HIV protease (no data), the prevention or treatment of infection by HIV (no data), and the treatment of AIDS (no data), are prepd.

IT 136465-90-2P 136522-17-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation) (prepn. of HIV protease inhibitors)

Searcher : Shears 308-4994

- IT 156879-13-9P 156928-12-0P 167539-21-1P  
 167539-26-6P 167539-27-7P 167817-13-2P  
 167817-14-3P 167817-15-4P 167817-16-5P  
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL  
 (Biological study); PREP (Preparation); USES (Uses)  
 (prepn. of HIV protease inhibitors)
- L9 ANSWER 34 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1995:755734 CAPLUS  
 DN 123:246040  
 TI Symmetry-based HIV protease inhibitors: rational design of  
 2-methylbenzamides as novel P2/P2' ligands  
 AU Randad, Ramnarayan S.; Lubkowska, Lucyna; Bhat, T. Narayana; Munshi,  
 Sanjeev; Gulnik, Sergei V.; Yu, Betty; Erickson, John W.  
 CS SAIC, Natl. Cancer Inst.-Frederick Cancer Res. and Development  
 Cent., Frederick, MD, 21702, USA  
 SO Bioorg. Med. Chem. Lett. (1995), 5(15), 1707-12  
 CODEN: BMCLE8; ISSN: 0960-894X  
 DT Journal  
 LA English  
 AB Readily accessible, non-peptidic, achiral 2-methylbenzamides were  
 designed to serve as P2/P2' ligands for symmetry-based inhibitors of  
 HIV-1 Protease. Introduction of 3-hydroxy substituent provided a  
 potent inhibitor 7 ( $K_i = 0.8$  nM).
- IT 168912-67-2P 168912-69-4P  
 RL: BAC (Biological activity or effector, except adverse); PRP  
 (Properties); SPN (Synthetic preparation); THU (Therapeutic use);  
 BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (symmetry-based HIV protease  
 inhibitors in relation to rational design of  
 methylbenzamides as novel P2/P2' ligands)
- IT 168912-64-9P 168912-65-0P 168912-66-1P  
 168912-68-3P  
 RL: BAC (Biological activity or effector, except adverse); SPN  
 (Synthetic preparation); THU (Therapeutic use); BIOL (Biological  
 study); PREP (Preparation); USES (Uses)  
 (symmetry-based HIV protease  
 inhibitors in relation to rational design of  
 methylbenzamides as novel P2/P2' ligands)
- IT 168912-63-8  
 RL: BAC (Biological activity or effector, except adverse); THU  
 (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (symmetry-based HIV protease  
 inhibitors in relation to rational design of  
 methylbenzamides as novel P2/P2' ligands)
- IT 134878-07-2 144163-44-0  
 RL: RCT (Reactant)  
 (symmetry-based HIV protease  
 inhibitors in relation to rational design of  
 Searcher : Shears 308-4994

methylbenzamides as novel P2/P2' ligands)

L9 ANSWER 35 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1995:694400 CAPLUS  
 DN 123:102125  
 TI Resistance of HIV type 1 to proteinase inhibitor Ro 31-8959  
 AU Eberle, Josef; Bechowsky, Brigitte; Rose, Dietlinde; Hauser, Ulrike;  
 Helm, Klaus Von Der; Guertler, Lutz; Nitschko, Hans  
 CS Max von Pettenkofer Institute, University Munich, Munich, D-80336,  
 Germany  
 SO AIDS Res. Hum. Retroviruses (1995), 11(6), 671-6  
 CODEN: ARHRE7; ISSN: 0889-2229  
 DT Journal  
 LA English  
 AB During replication of human immunodeficiency virus type 1 (HIV-1),  
 proteolytic cleavage of Gag and Gag-Pol precursor proteins into  
 different functional protein subunits is catalyzed by the viral  
 proteinase, and this enzyme is the target of the antiviral  
 proteinase inhibitor, Ro 31-8959. We investigated in vitro which  
 HIV mutants with reduced sensitivity to Ro 31-8959 emerged during  
 proteinase inhibition treatment; from three different HIV-1 strains,  
 comparable progeny virus resistant to proteinase inhibitor were  
 found, whereas the same exptl. protocol detected no resistant HIV-2  
 mutants. Mol. anal. of the mutations underlying resistance revealed  
 a multistep mechanism in which an amino acid exchange at position 48  
 of the proteinase from glycine to valine seemed to play an initial  
 role. This amino acid exchange was common to all resistant  
 isolates, and in all expts. preceded further exchanges at position  
 90 (leucine to methionine) and/or at position 54 (isoleucine to  
 valine). For wild-type strains the 90% inhibitory concns. of Ro  
 31-8959 were close to 20 nM, whereas HIV-1 mutants with all 3 amino  
 acid exchanges had more than 50-fold increased 90% inhibitory  
 concns. (above 1000 nM). The primary event (Gly-48 to valine)  
 occurs at the hinge of the flaps of the proteinase, thus hampering  
 entry of the inhibitor to the active center and suggesting steric  
 hindrance. Detailed knowledge of this stereotypic process could  
 open inhibitor design, thus preventing conceivable escape of  
 resistant virus on proteinase inhibitor action.  
 IT 127779-20-8  
 RL: ADV (Adverse effect, including toxicity); BAC (Biological  
 activity or effector, except adverse); BIOL (Biological study)  
 (resistance of HIV type 1 to proteinase  
 inhibitor Ro 31-8959)

L9 ANSWER 36 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1995:609444 CAPLUS  
 DN 123:102047  
 TI HIV protease inhibitor HOE/BAY 793, structure-activity relationships  
 in a series of C2-symmetric diols  
 Searcher : Shears 308-4994



AU Budt, Karl-Heinz; Peyman, Anusch; Hansen, Jutta; Knolle, Jochen; Meichsner, Christoph; Paessens, Arno; Ruppert, Dieter; Stowasser, Bernd

CS Hoechst AG, Pharma Res., Frankfurt, 65926, Germany

SO Bioorg. Med. Chem. (1995), 3(5), 559-71  
CODEN: BMECEP; ISSN: 0968-0896

DT Journal

LA English

AB A detailed structure-activity relation of C2-sym. diol inhibitors of HIV-1 protease leads to the inhibitor HOE/BAY 793 which is very potent in the inhibition of the enzyme and in the inhibition of viral replication in HIV infected cell culture (IC50: 0.3 nM; EC50: 3 nM). There are well defined steric requirements for the design of the side chains P1-P3 of the inhibitors. In addn., all three side chains need to be lipophilic. While the enzyme tolerates hydrophilic substituents in some cases, drastic redns. in anti-HIV activity are obsd. in cell culture after substitution with hydrophilic groups, which is most likely due to insufficient cell penetration of these compds.

IT 137755-28-3P 165406-33-7P  
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(HIV protease inhibitor HOE/BAY 793  
and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

IT 137755-25-0P 137755-42-1P 137755-47-6P  
137755-48-7P 137808-03-8P 137808-09-4P  
137808-16-3P 137821-89-7P 137828-32-1P  
137828-36-5P 137828-38-7P 137853-70-4P  
165406-34-8P 165406-35-9P 165406-37-1P  
165406-39-3P 165406-40-6P 165406-41-7P  
165406-42-8P 165406-43-9P 165406-44-0P  
165406-45-1P 165406-46-2P 165406-47-3P  
165406-48-4P 165406-51-9P 165406-52-0P  
165876-29-9P 165876-32-4P 165876-34-6P  
165876-35-7P  
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(HIV protease inhibitor HOE/BAY 793  
and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

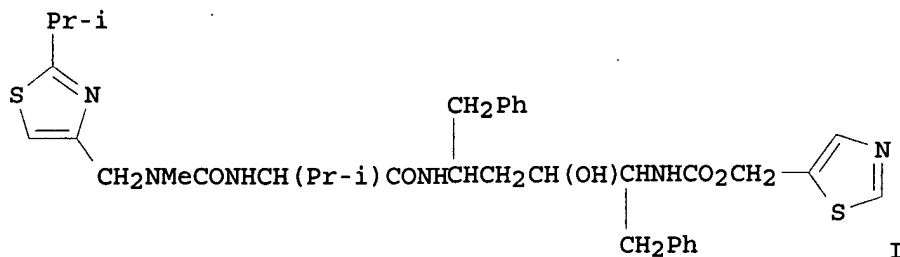
IT 129491-63-0 137828-50-3 165876-33-5  
RL: RCT (Reactant)  
(HIV protease inhibitor HOE/BAY 793  
and structure-activity relationships in a series of C2-sym. diol analogs in relation to antiviral activity in human cells)

Searcher : Shears 308-4994

IT 129491-64-1P 129491-65-2P 134805-49-5P  
 137755-20-5P 137808-10-7P 137808-17-4P  
 137894-61-2P 165406-31-5P 165406-32-6P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)  
 (HIV protease inhibitor HOE/BAY 793  
 and structure-activity relationships in a series of C2-sym. diol  
 analogs in relation to antiviral activity in human cells)

L9 ANSWER 37 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1995:532332 CAPLUS  
 DN 122:299083  
 TI Pharmaceutical composition of HIV protease inhibitors  
 IN Al-Razzak, Laman A.; Marsh, Kennan C.; Manning, Lourdes P.; Kaul,  
 Dilip  
 PA Abbott Laboratories, USA  
 SO PCT Int. Appl., 84 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9507696	A1	19950323	WO 94-US9788	19940830
	W: AU, CA, JP, KR				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2167412	AA	19950323	CA 94-2167412	19940830
	AU 9477176	A1	19950403	AU 94-77176	19940830
	AU 695516	B2	19980813		
	EP 719142	A1	19960703	EP 94-927973	19940830
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	JP 09502715	T2	19970318	JP 94-509212	19940830
	US 5725878	A	19980310	US 95-435009	19950504
PRAI	US 93-120886		19930913		
	US 94-188511		19940128		
	US 94-267331		19940628		
	US 94-288873		19940815		
	WO 94-US9788		19940830		
	US 95-402690		19950313		
OS	MARPAT 122:299083				
GI					



AB A pharmaceutical compn. comprising a soln. of an HIV protease-inhibiting compd. in a pharmaceutically acceptable org. solvent comprising an alc., optionally combined with an acid or a combination of acids, shows high oral bioavailability. The soln. can optionally be encapsulated in hard gelatin capsules or soft elastic gelatin capsules, or granulated with a pharmaceutically acceptable granulating agent. Thus, hard gelatin capsules contained HIV protease inhibitor I 8.8, propylene glycol 82.3, EtOH 3.5, HCl 0.9, and water 4.4 wt.%. I was prepd. in multiple steps beginning from N-benzyloxycarbonyl-L-phenylalaninol.

IT 155213-67-5 162990-01-4 162990-02-5

RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(pharmaceutical compn. of HIV protease inhibitors)

IT 143838-10-2P 144164-10-3P

RL: BYP (Byproduct); SPN (Synthetic preparation); PREP (Preparation)  
(pharmaceutical compn. of HIV protease inhibitors)

IT 156732-15-9

RL: RCT (Reactant)  
(pharmaceutical compn. of HIV protease inhibitors)

IT 137649-69-5P 144141-68-4P 144163-44-0P

144163-85-9P 144164-11-4P 162849-93-6P

162849-95-8P 162990-03-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)  
(pharmaceutical compn. of HIV protease inhibitors)

L9 ANSWER 38 OF 82 CAPLUS COPYRIGHT 1999 ACS

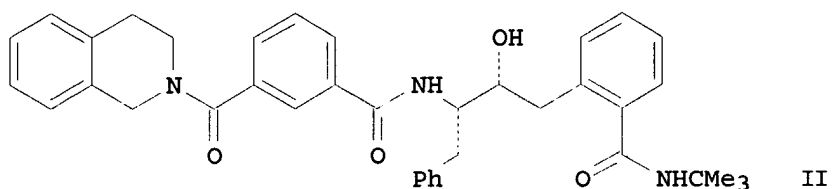
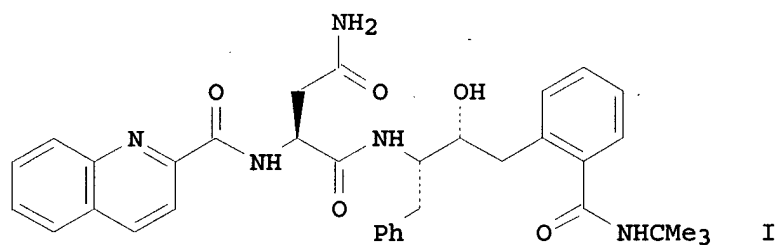
AN 1995:519323 CAPLUS

DN 122:305873

TI Isophthalic acid derivatives: amino acid surrogates for the inhibition of HIV-1 protease

AU Kaldor, Stephen W.; Dressman, Bruce A.; Hammond, Marlys; Appelt, Krzysztof; Burgess, Jeffrey; Lubbehusen, Penny P.; Muesing, Mark A.;  
Searcher : Shears 308-4994

Hatch, Steven D.; Wiskerchen, Mary Ann; Baxter, Angela J.  
 CS Lilly Res. Lab., Eli Lilly Co., Indianapolis, 46285, India  
 SO Bioorg. Med. Chem. Lett. (1995), 5(7), 721-6  
 CODEN: BMCLE8; ISSN: 0960-894X  
 DT Journal  
 LA English  
 OS CASREACT 122:305873  
 GI



AB Using the x-ray crystal structure of the inhibitor I complexed to HIV-1 protease, a new series of HIV-1 protease inhibitors was developed incorporating substituted isophthalic acid derivs. as amino acid surrogates. Through iterative structure-based design, the lead compd. II was optimized to produce a variety of non-peptide HIV-1 protease inhibitors with significant antiviral activity. In contrast to I, several members of this series exhibit significant oral absorption in animals.

IT 163462-22-4P 163462-23-5P

RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (HIV-1 protease inhibitors contg.  
 isophthalic acid derivs. as amino acid surrogates)

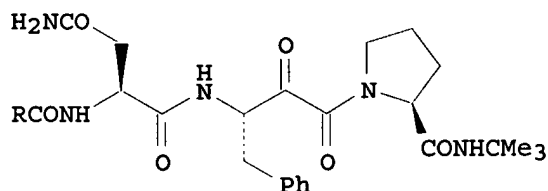
L9 ANSWER 39 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1995:502552 CAPLUS

DN 123:256243

TI Synthesis of a novel C2-symmetrical (2S,5S)-2,5-bis-[(1,1-  
 Searcher : Shears 308-4994

- dimethylethoxy)carbonylamino]-1,6-diphenylhex-3-ene: applications in the synthesis of potential HIV protease inhibitors
- AU Rao, A. V. Rama; Gurjar, Mukund K.; Pal, Shashwati; Pariza, Richard J.; Chorghade, Mukund S.
- CS Indian Institute Chemical Technology, Hyderabad, 500 007, India
- SO Tetrahedron Lett. (1995), 36(14), 2505-8  
CODEN: TELEAY; ISSN: 0040-4039
- DT Journal
- LA English
- OS CASREACT 123:256243
- AB The synthesis of a novel and versatile (2S,5S)-2,5-bis[(1,1'-dimethylethoxy)carbonylamino]-1,6-diphenylhex-3-ene (2) based on Julia's olefination strategy coupled with its application in stereoselective preps. of HIV protease inhibitors has been discussed.
- IT 129491-63-0P 129491-64-1P 144141-82-2P  
144239-47-4P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(synthesis of potential HIV protease inhibitors)
- L9 ANSWER 40 OF 82 CAPLUS COPYRIGHT 1999 ACS
- AN 1995:440143 CAPLUS
- DN 123:112687
- TI Synthesis and human immunodeficiency virus (HIV)-1 protease inhibitory activity of tripeptide analogs containing a dioxoethylene moiety
- AU Kitazaki, Tomoyuki; Asano, Tsuneo; Kato, Koichi; Kishimoto, Shoji; Itoh, Katsumi
- CS Pharmaceutical Research Laboratories III, Takeda Chemical Industries, Ltd., Osaka, 532, Japan
- SO Chem. Pharm. Bull. (1994), 42(12), 2636-40  
CODEN: CPBTAL; ISSN: 0009-2363
- DT Journal
- LA English
- GI



- AB Tripeptide analogs I (R = PhCH<sub>2</sub>O, 2-quinolyl), contg. a dioxoethylene moiety, were designed based on the characteristic
- Searcher : Shears 308-4994

structure of the naturally occurring human immunodeficiency virus (HIV)-1 protease inhibitors RPI-856 A, B, C and D. I showed high inhibitory activity, comparable to that of RPI-856 A, against HIV-1 protease in vitro.

IT 141171-80-4P

RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(synthesis and human immunodeficiency virus-1 protease inhibitory activity of tripeptide analogs contg. a dioxoethylene moiety)

IT 141171-73-5P 152843-00-0P 165522-25-8P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation) (synthesis and human immunodeficiency

virus-1 protease inhibitory activity of tripeptide analogs contg. a dioxoethylene moiety)

IT 139758-12-6P 141171-72-4P 152886-87-8P

153380-43-9P 165522-26-9P 165522-27-0P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation) (synthesis and human immunodeficiency

virus-1 protease inhibitory activity of tripeptide analogs contg. a dioxoethylene moiety)

L9 ANSWER 41 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1995:438973 CAPLUS

DN 122:286354

TI Limited sequence diversity of the HIV type 1 protease gene from clinical isolates and in vitro susceptibility to HIV protease inhibitors

AU Winslow, Dean L.; Stack, Sylvia; King, Robert; Scarnati, Helen; Bincsik, Arlene; Otto, Michael J.

CS Du Pont-Merck Pharmaceutical Company, Glenolden, PA, USA

SO AIDS Res. Hum. Retroviruses (1995), 11(1), 107-13

CODEN: ARHRE7; ISSN: 0889-2229

DT Journal

LA English

AB Proviral DNAs from 3 lab. strains and 21 clin. isolates of HIV-1 were extd. from infected cells after proteinase K digestion and the protease gene was PCR amplified and sequenced directly by the Sanger method. In vitro susceptibilities of the virus isolates to protease inhibitors were detd. by the ACTG/DoD consensus assay. Four different HIV protease inhibitors were tested including P9941, a C2 sym. diol (Du Pont-Merck); A80987, an asym. mono-ol (Abbott); XM323, a cyclic urea (Du Pont-Merck); and Ro31-8959, an asym. hydroxyethylene isostere (Roche). Maximum sequence variation was 10% at both the nucleic and amino acid levels. Purine-purine substitutions were most common. Five noncontiguous regions were conserved across all isolates and corresponded to amino acids 1-9

Searcher : Shears 308-4994

(amino terminal), 21-32 (catalytic site), 47-56 ("flap" region), 78-88 (substrate-binding region), and 94-99 (carboxy terminal). All clin. isolates demonstrated in vitro susceptibility to the protease inhibitors. There was no significant difference between the susceptibility of the ref. strains and the clin. isolates. These data suggest that the variable regions of protease do not contain sites that are important for interactions with the inhibitors tested.

IT 127779-20-8 140196-60-7, P9941

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(four different HIV protease

inhibitors were tested including P9941, a C2 sym. diol;

A80987, an asym. mono-ol; XM323, a cyclic urea; and Ro31-8959, an asym. hydroxyethylene isostere; all clin. isolates demonstrated in vitro susceptibility)

L9 ANSWER 42 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1995:264545 CAPLUS

DN 122:55900

TI Inhibitors of HIV protease useful for the treatment of AIDS.

IN Jungheim, Louis Nickolaus; Shepherd, Timothy Alan

PA Lilly, Eli, and Co., USA

SO Eur. Pat. Appl., 61 pp.

CODEN: EPXXDW

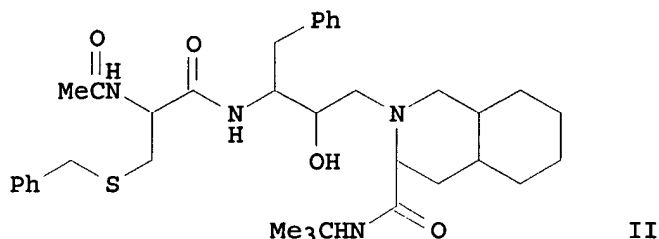
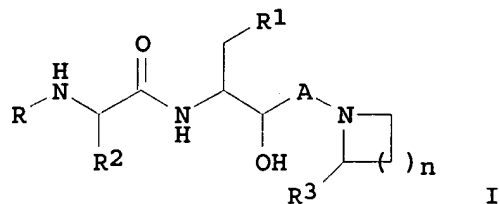
DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 604185	A1	19940629	EP 93-310359	19931220
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	US 5733906	A	19980331	US 93-134329	19931012
	ZA 9309475	A	19950619	ZA 93-9475	19931217
	NO 9304719	A	19940623	NO 93-4719	19931220
	AU 9352528	A1	19940707	AU 93-52528	19931220
	AU 667146	B2	19960307		
	HU 69693	A2	19950928	HU 93-3679	19931220
	IL 108092	A1	19980615	IL 93-108092	19931220
	CA 2112042	AA	19940623	CA 93-2112042	19931221
	FI 9305778	A	19940623	FI 93-5778	19931221
	JP 06271534	A2	19940927	JP 93-322750	19931221
	BR 9305162	A	19941101	BR 93-5162	19931221
	CN 1094399	A	19941102	CN 93-112962	19931221
PRAI	US 92-995256		19921222		
	US 93-134329		19931012		
OS	MARPAT 122:55900				
GI					

Searcher : Shears 308-4994



AB Oligopeptide analogs I (R1 = aryl, alkyl, alkylthio, etc.; R2 = amino acid side chain, etc.; ) were disclosed. I are HIV protease inhibitors useful for the treatment of HIV infection and AIDS. Claimed example compd., [2R-(2R\*,3S\*,6S\*,4a'S\*,8a'S\*)]-N-(tert-butyl)-2-[2-hydroxy-3-(phenylmethyl)-4-aza-5-oxo-6-(ethanoylamino)-7-[(phenylmethyl)thio]heptyl]decahydro-3-isoquinolinecarboxamide (II) was prepd.

IT 159878-24-7P 159878-25-8P 159878-26-9P  
159878-27-0P 159878-28-1P 159878-29-2P  
159878-30-5P 159878-31-6P 159991-28-3P  
159991-29-4P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, as HIV protease inhibitor  
virucide)

L9 ANSWER 43 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1995:5849 CAPLUS

DN 123:32926

TI The Development of Cyclic Sulfolanes as Novel and High-Affinity P2 Ligands for HIV-1 Protease Inhibitors

AU Ghosh, Arun K.; Lee, Hee Yoon; Thompson, Wayne J.; Culberson, Chris; Holloway, M. Katharine; McKee, Sean P.; Munson, Peter M.; Duong, Tien T.; Smith, Anthony M.; et al.

CS Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA

SO J. Med. Chem. (1994), 37(8), 1177-88

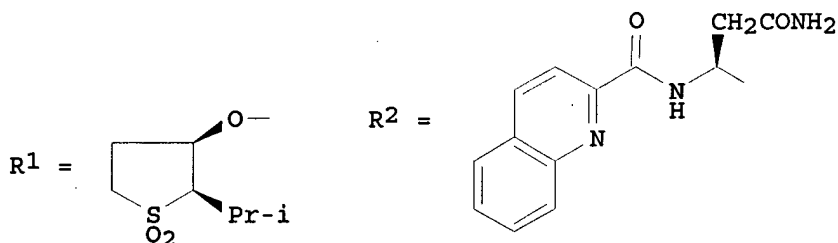
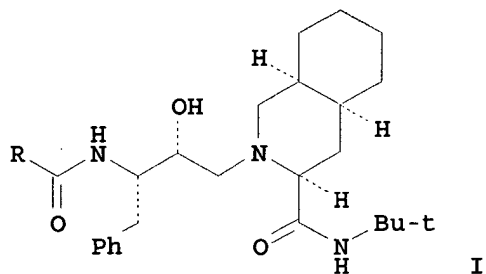
CODEN: JMCMAR; ISSN: 0022-2623

DT Journal

Searcher : Shears 308-4994



LA English  
OS CJACS  
GI



AB Design and synthesis of a novel series of protease inhibitors incorporating conformationally constrained cyclic ligands for the S2-substrate binding site of HIV-1 protease is described. Inhibitor I (R = R<sub>1</sub>) (IC<sub>50</sub> 3.5 nM, CIC<sub>95</sub> 50 .+- . 14 nM) has comparable in vitro antiviral potency to the current clin. candidate I (R = R<sub>2</sub>) (Ro 31-8959) but of reduced mol. wt. due to the exclusion of the P<sub>3</sub> quinoline ligand. Also, it has been demonstrated that octahydropyrindene is an effective replacement for decahydroisoquinoline.

IT 147949-29-9P 147949-30-2P 147949-31-3P  
147949-32-4P 147949-33-5P 147949-34-6P  
147949-35-7P 147977-17-1P 147977-18-2P  
147977-19-3P 147977-20-6P 147977-21-7P  
147977-22-8P 150330-55-5P 150330-67-9P  
150406-19-2P 150406-23-8P 161404-82-6P  
161511-64-4P 162776-43-4P 162776-45-6P  
162776-47-8P 162776-49-0P 162776-50-3P  
162870-64-6P 162870-65-7P 162870-66-8P  
162870-67-9P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation) (prepn. and HIV protease-inhibiting activity of acylaminobutyldecahydroisoquinolines)

Searcher : Shears 308-4994

IT 136465-90-2P 136522-17-3P 147949-28-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)  
(prepn. and HIV protease-inhibiting  
activity of acylaminobutyldecahydroisoquinolines)

L9 ANSWER 44 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1994:621038 CAPLUS

DN 121:221038

TI Structure-Based Design of HIV-1 Protease Inhibitors: Replacement of  
Two Amides and a 10.pi.-Aromatic System by a Fused  
Bis-tetrahydrofuran

AU Ghosh, Arun K.; Thompson, Wayne J.; Fitzgerald, Paula M. D.;  
Culberson, J. Chris; Axel, Melinda G.; McKee, Sean P.; Huff, Joel  
R.; Anderson, Paul S.

CS Department of Medicinal Chemistry, Merck Research Laboratories, West  
Point, PA, 19486, USA

SO J. Med. Chem. (1994), 37(16), 2506-8

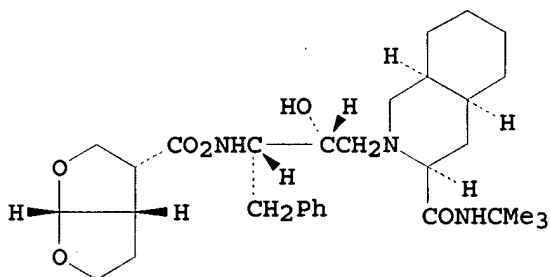
CODEN: JMCMAR; ISSN: 0022-2623

DT Journal

LA English

OS CJACS

GI



I

AB The structure-based design of a conformationally constrained fused  
bistetrahydrofuran effectively replaces 2 amide bonds and a  
10.pi.-arom. system of the present clin. candidate, Ro 31-8959. The  
inhibitor (I) (IC50 = 1.8 nM,; CIC95 = 46 nM) thus obtained, showed  
comparable in vitro antiviral activities to inhibitors in the  
hydroxyethylamine class with both P2 and P3 ligands. To obtain  
information regarding the ligand binding site interactions, a single  
crystal of the inhibitor I complexed with HIV-1 protease was  
generated, and the 3-dimensional structure was detd. by x-ray  
diffraction to 2.10 .ANG. resohn. Interestingly, the oxygen-1 and  
oxygen-6 of the bis-tetrahydrofuran ligand are within hydrogen  
bonding distance to the Asp 29 NH and Asp 30 NH present in the S2  
binding domain of the HIV-1 protease. The design and synthesis of

Searcher : Shears 308-4994

such a high affinity ligand led to improved aq. soly. and redn. in mol. wt. due to exclusion of the P3 ligand.

IT 127779-20-8, Ro 31-8959

RL: BIOL (Biological study)

(HIV-1 protease inhibitor, analogs  
prepn in relation to)

IT 156879-13-9P 156928-12-0P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, as HIV-1 protease  
inhibitor)

L9 ANSWER 45 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1994:499067 CAPLUS

DN 121:99067

TI Structure-activity relationships of tripeptide HIV protease  
inhibitors containing the hydroxymethylcarbonyl isostere

AU Enomoto, Hiroshi; Mimoto, Tsutomu; Kisanuki, Sumitsugu; Kimura,  
Tooru; Hattori, Naoko; Kageyama, Seiji; Mitsuya, Hiroaki; Akaji,  
Kenichi; Kiso, Yoshiaki

CS Dep. Med. Chem., Kyoto Pharm. Univ., Kyoto, 607, Japan

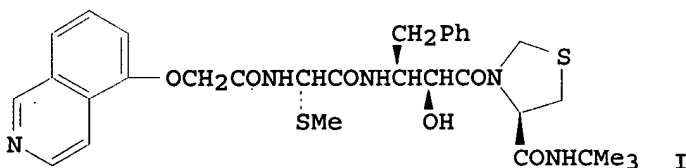
SO Pept. Chem. (1993), 31st, 181-4

CODEN: PECHDP; ISSN: 0388-3698

DT Journal

LA English

GI



AB The inhibitors which had substitution of amino acid at P2 and/or P1 position of KNI-272 (I) with more lipophilic or hydrophilic residues were examd. in an enzyme inhibitory assay and antiviral assay. All the compds. inhibited HIV protease as strongly as I, but there was a difference in antiviral activities of those compds. Low antiviral activities were shown by more hydrophilic compds. than I, while more lipophilic ones showed potent activities comparable to I.

IT 138258-64-7, KNI 93 139694-65-8, KNI 102

RL: BIOL (Biological study)

(HIV-1 protease inhibitor,  
structure in relation to)

L9 ANSWER 46 OF 82 CAPLUS COPYRIGHT 1999 ACS

Searcher : Shears 308-4994

AN 1994:428001 CAPLUS  
DN 121:28001  
TI A rapid and simple screening method for HIV-1 protease inhibitors  
using recombinant Escherichia coli  
AU Kaneto, Rei; Kojima, Ikuo; Shibamoto, Norio; Nishida, Hiroshi;  
Okamoto, Rokuro; Akagawa, Hisayoshi; Mizuno, Satoshi  
CS Cent. Res. Lab., Mercian Corp., Fujisawa, 251, Japan  
SO J. Antibiot. (1994), 47(4), 492-5  
CODEN: JANTAJ; ISSN: 0021-8820  
DT Journal  
LA English  
AB This report deals with construction of a recombinant plasmid  
carrying the chem. synthesized HIV-1 protease gene and its  
successful expression in Escherichia coli. A screening system for  
HIV-1 protease inhibitors from microbial metabolite origin was  
established by using the expressed protease and a peptide analogous  
to one of the HIV-1 polyproteins. A novel screening system of  
naturally occurring protease inhibitors was also established by  
using E. coli carrying the recombined plasmid. A comparison of th 2  
screening systems is made and their advantages are discussed.  
IT 127779-20-8  
RL: USES (Uses)  
(HIV-1 protease inhibition by)

L9 ANSWER 47 OF 82 CAPLUS COPYRIGHT 1999 ACS  
AN 1994:289408 CAPLUS  
DN 120:289408  
TI Three-dimensional QSAR of human immunodeficiency virus (I) protease  
inhibitors. 1. A CoMFA study employing experimentally-determined  
alignment rules  
AU Waller, Chris L.; Oprea, Tudor I.; Giolitti, Alessandro; Marshall,  
Garland R.  
CS Cent. Mol. Des., Washington Univ., St. Louis, MO, 63130, USA  
SO J. Med. Chem. (1993), 36(26), 4152-60  
CODEN: JMCMAR; ISSN: 0022-2623  
DT Journal  
LA English  
OS CJACS  
AB Comparative mol. field anal. (CoMFA), a 3-dimensional, quant.  
structure-activity relationship (QSAR) paradigm, was used to exam.  
the correlations between the calcd. physicochem. properties and in  
the vitro activities of a series of human immunodeficiency virus  
(HIV-1) protease inhibitors. The training set consisted of 59 mols.  
from five structurally-diverse transition-state isostere classes:  
hydroxyethylamine, statine, norstatine, keto amide, and  
dihydroxyethylene. The availability of x-ray crystallog. data for  
at least one representative from each class bound to the protease  
provided information regarding not only the active conformation of  
each ligand but also, via superimposition of protease backbones, the  
Searcher : Shears 308-4994

relative positions of each ligand with respect to one another in the active site of the enzyme. Once aligned, these mols. served as templates on which addnl. congeners were field-fit minimized. Addnl. alignment rules were derived from minimization of the ligands in the active site of the semirigid protease. The predictive ability of each resultant model was evaluated using a test set comprised of mols. contg. a novel transition-state isostere: hydroxyethylurea. Crystallog. studies indicated an unexpected binding mode for this series of compds. which precluded the use of the field-fit minimization alignment technique. The test set mols. were, therefore, subjected to a limited systematic search in conjunction with active-site minimization. The conformer of each mol. expressing the lowest interaction energy with the active site was included in the test set. Field-fit minimization of neutral mols. to crystal ligands and active-site minimizations of protonated ligands yielded predictive correlations for HIV-1 protease inhibitors. The use of crystallog. data in the detn. of alignment rules and field-fit minimization as a mol. alignment tool in the absence of direct exptl. data regarding binding modes is strongly supported by these results.

IT 127749-95-5 127779-20-8 132234-38-9  
 132234-39-0 136522-18-4 137515-64-1  
 137622-86-7 137622-87-8 137693-11-9  
 139694-65-8 139758-12-6 141171-72-4  
 141171-73-5 141171-74-6 141171-76-8  
 141171-77-9 141171-78-0 141171-79-1  
 141171-80-4 141171-81-5 141197-75-3  
 141269-68-3 153126-40-0 153126-41-1  
 153220-54-3 153220-55-4

RL: BIOL (Biological study)  
 (human immunodeficiency virus 1  
 protease inhibition by, QSAR of)

L9 ANSWER 48 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1994:245776 CAPLUS  
 DN 120:245776

TI Preparation of cyclic amides of 3-amino-2-hydroxycarboxylic acids as HIV protease inhibitors

IN Krantz, Alexander; Tam, Tim Fat; Castelhana, Arlindo Lucas; Nestor, John Joseph, Jr.

PA Syntex (U.S.A.), Inc., USA

SO PCT Int. Appl., 76 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

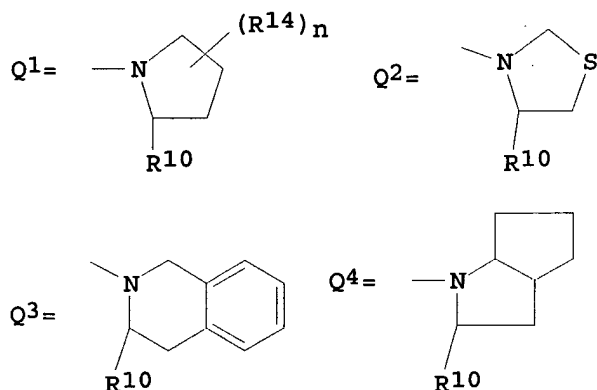
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	---	-----	-----	-----
PI	WO 9313066	A1	19930708	WO 92-US10772	19921218
			Searcher	: Shears	308-4994

W: AU, CA, FI, HU, JP, KR, NO, NZ

RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT,

SE

AU 9332782	A1 19930728	AU 93-32782	19921218
ZA 9209869	A 19940620	ZA 92-9869	19921218
PRAI US 91-812905	19911220		
WO 92-US10772	19921218		
OS MARPAT 120:245776			
GI			



AB R1R2NCHR3CONHCHR4CR5R6COR7 [R1 = (ar)alkoxycarbonyl, (substituted) aralkanoyl, aroyl, heterocyclylcarbonyl, aryloxyalkanoyl, carbamoyl, heterocyclyloxyalkanoyl; R2, R5 = H; R3 = (substituted) alkyl, R4 = (substituted) aryl, aralkyl; R6 = OH; R5R6 = O; R1 = Q1-Q4, etc.; n = 0-2; R10 = alkoxycarbonyl, (substituted) carbamoyl; R14 = OH, alkyl, alkoxy, Ph], were prepd. Thus, N'-tert-Bu prolinamide (prepn. given) was coupled with (2S,3S)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid using EDCI/hydroxybenzotriazole in DMF to give 1-[(2S,3S)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-N'-tert-butyl-L-prolinamide. I inhibited HIV protease with IC50 = 0.49-30 nM. I dosage formulations are given.

IT 139694-65-8P 139758-12-6P 141171-73-5P  
 141171-74-6P 141171-76-8P 141171-77-9P  
 141171-78-0P 141171-79-1P 141171-80-4P  
 141171-81-5P 141197-75-3P 143934-35-4P  
 143934-48-9P 144780-35-8P 144830-03-5P  
 153290-07-4P 153290-08-5P 153290-10-9P  
 153290-11-0P 153290-12-1P 153290-13-2P  
 153290-14-3P 153290-15-4P 153290-16-5P  
 153290-17-6P 153290-18-7P 153290-19-8P  
 153290-20-1P 153290-21-2P 153290-22-3P  
 153290-23-4P 153290-24-5P 153290-25-6P

Searcher : Shears 308-4994

153290-26-7P 153290-27-8P 153290-28-9P  
 153290-29-0P 153290-31-4P 153290-32-5P  
 153290-33-6P 153290-34-7P 153290-35-8P  
 153290-36-9P 153290-37-0P 153290-38-1P  
 153290-39-2P 153290-40-5P 153290-41-6P  
 153290-42-7P 153290-43-8P 153290-44-9P  
 153290-45-0P 153290-46-1P 153290-47-2P  
 153290-48-3P 153290-49-4P 153290-50-7P  
 153290-51-8P 153290-52-9P 153313-34-9P  
 153380-12-2P 153380-13-3P 153380-14-4P  
 153380-16-6P 153380-17-7P 153380-18-8P  
 153380-19-9P 153380-20-2P 153380-21-3P  
 153380-22-4P 153380-23-5P 153380-24-6P  
 153380-25-7P 153380-26-8P 153380-27-9P  
 153380-28-0P 153380-29-1P 153380-30-4P  
 153380-31-5P 153381-18-1P 153546-68-0P

RL: BAC (Biological activity or effector, except adverse); SPN  
 (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (prepn. of, as HIV protease inhibitor  
 )

L9 ANSWER 49 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1994:208003 CAPLUS

DN 120:208003

TI Characterization of human immunodeficiency virus type 1 variants  
 with increased resistance to a C2-symmetric protease inhibitor

AU Ho, David D.; Toyoshima, Takuo; Mo, Hongmei; Kempf, Dale J.;  
 Norbeck, Daniel; Chen, Chih Ming; Wideburg, Norman E.; Burt, Stan  
 K.; Erickson, John W.; Singh, Mandaleshwar K.

CS Sch. Med., New York Univ., New York, NY, 10016, USA

SO J. Virol. (1994), 68(3), 2016-20

CODEN: JOVIAM; ISSN: 0022-538X

DT Journal

LA English

AB Inhibitors of the human immunodeficiency virus type 1 protease  
 represent a promising class of antiviral drugs for the treatment of  
 AIDS, and several are now in clin. trials. Here, the authors report  
 the in vitro selection of viral variants with decreased sensitivity  
 to a C2-sym. protease inhibitor (A-77003). The authors show that a  
 single amino acid substitution (Arg to Gln or Lys) at position 8 of  
 the protease results in a substantial decrease in the inhibitory  
 activity of the drug on the enzyme and a comparable increase in  
 viral resistance. These findings, when analyzed by using the  
 three-dimensional structure of the protease-drug complex, provide a  
 strategic guide for the future development of inhibitors of the  
 human immunodeficiency virus type 1 protease.

IT 127779-20-8 129491-65-2, A 76215

134805-77-9, A 76889 134878-16-3, A 76928

134878-17-4, A 77003

Searcher : Shears 308-4994

RL: BIOL (Biological study)  
 (HIV-1 protease inhibitory activity  
 of, enzyme structure and resistance to antiviral action in  
 relation to)

L9 ANSWER 50 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1994:191116 CAPLUS

DN 120:191116

TI Process for the preparation of a substituted diaminodiol

IN Sowin, Thomas J.; Hannick, Steven M.; Doherty, Elizabeth M.; Sato,  
 Takahiro; Suzuki, Takayuki

PA Abbott Laboratories, USA

SO PCT Int. Appl., 44 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9323361	A1	19931125	WO 93-US4403	19930510
	W: CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

PRAI US 92-885575 19920519

OS MARPAT 120:191116

AB Title compds. (I; PhCH<sub>2</sub>CH(R<sub>3</sub>NH)CH(OH)CH(OH)CH(R<sub>3</sub>NH)CH<sub>2</sub>Ph) (wherein  
 R<sub>3</sub> = H, N-protectant) useful as HIV protease inhibitor (no data),  
 are prepd. L-Phenylalanine Me ester-HCl (prepn. given) in CHCl<sub>3</sub> was  
 cooled to 0.degree., Na<sub>2</sub>CO<sub>3</sub> was added followed by ClCO<sub>2</sub>CH<sub>2</sub>Ph to give  
 the benzoyloxycarbony deriv., which was treated with LiAlH<sub>4</sub> to the  
 alaninol, treated with (COCl)<sub>2</sub> to give the alaninal and in turn  
 reacted with VCl<sub>3</sub>(THF)<sub>3</sub> and Zn dust to give a mixt. of diols which  
 were treated with acetone and concd. H<sub>2</sub>SO<sub>4</sub> to give (2S,3R,4R,5S)-I  
 (R<sub>3</sub> = PhCH<sub>2</sub>O<sub>2</sub>C).

IT 134878-07-2P 134878-17-4P 137649-69-5P

RL: BAC (Biological activity or effector, except adverse); SPN  
 (Synthetic preparation); THU (Therapeutic use); BIOL (Biological  
 study); PREP (Preparation); USES (Uses)  
 (prepn. of, as HIV protease inhibitor  
 )

L9 ANSWER 51 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1994:153056 CAPLUS

DN 120:153056

TI Human Immunodeficiency Virus Type 1 Protease Inhibitors: Evaluation  
 of Resistance Engendered by Amino Acid Substitutions in the Enzyme's  
 Substrate Binding Site

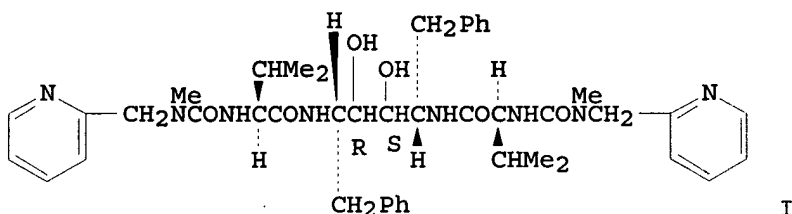
AU Sardana, Vinod V.; Schlabach, Abner J.; Graham, Pia; Bush, Bruce L.;  
 Condra, Jon H.; Culberson, J. Chris; Gotlib, Leah; Graham, Donald

Searcher : Shears 308-4994



J.; Kohl, Nancy E.; et al.  
 CS Department of Virus and Cell Biology, Merck Research Laboratories,  
 West Point, PA, 19486, USA  
 SO Biochemistry (1994), 33(8), 2004-10  
 CODEN: BICHAW; ISSN: 0006-2960  
 DT Journal  
 LA English  
 OS CJACS  
 AB The human immunodeficiency virus type 1 (HIV-1) protease is a  
 homodimeric aspartyl endopeptidase that is required for virus  
 replication. A no. of specific, active-site inhibitors for this  
 enzyme have been described. Many of the inhibitors exhibit  
 significant differences in activity against the HIV-1 and HIV type 2  
 (HIV-2) enzymes. An initial study was conducted to ascertain the  
 HIV-1 protease's potential to lose sensitivity to several test  
 inhibitors while retaining full enzymic activity. The substrate  
 binding sites of the HIV-1 and HIV-2 enzymes are almost fully  
 conserved, except for four amino acid residues at positions 32, 47,  
 76, and 82. Accordingly, recombinant mutant type 1 proteases were  
 constructed that contained the cognate type 2 residue at each of  
 these four positions. The substitution at position 32 resulted in a  
 significant adverse effect on inhibitor potency. However, this  
 substitution also mediated a noted decrease in the Km of the  
 substrate. Individual substitutions at the remaining three  
 positions, as well as a combination of all four substitutions, had  
 very little effect on enzyme activity or inhibitor susceptibility.  
 Hence, the four studied active site residues are insufficient to be  
 responsible for differences in inhibitor sensitivity between the  
 HIV-1 and HIV-2 proteases and are unlikely to contribute to the  
 generation of inhibitor-resistant mutant HIV-1 protease.  
 IT 127779-20-8, Ro 31-8959  
 RL: BIOL (Biological study)  
 (HIV protease inhibition by,  
 resistance to, substitution mutation effect on)  
 L9 ANSWER 52 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1994:152978 CAPLUS  
 DN 120:152978  
 TI Influence of Stereochemistry on Activity and Binding Modes for C2  
 Symmetry-Based Diol Inhibitors of HIV-1 Protease  
 AU Hosur, Madhusoodan V.; Bhat, T. Narayana; Kempf, Dale J.; Baldwin,  
 Eric T.; Liu, Beishan; Gulnik, Sergei; Wideburg, Norman E.; Norbeck,  
 Daniel W.; Appelt, Krzysztof; Erickson, John W.  
 CS Frederick Biomedical Supercomputing Center, PRI/DynCorp, Frederick,  
 MD, 21702, USA  
 SO J. Am. Chem. Soc. (1994), 116(3), 847-55  
 CODEN: JACSAT; ISSN: 0002-7863  
 DT Journal  
 LA English

OS CJACS  
GI



AB The incorporation of C2 symmetry has become a useful paradigm in the design of active site inhibitors for HIV-1 protease (HIV PR) and has led to the design of a series of highly potent, C2 symmetry-based, diol-contg. inhibitors of HIV PR, one of which, A-77003 (I), has reached clin. trials. However, the stereochem. of the diol core influences protease inhibition and antiviral activity in a manner that is not well understood. The authors analyzed the crystal structures of a diastereomeric series of C2 symmetry-based diol inhibitors, along with a deshydroxy analog, bound to HIV PR and found that the stereochem. of the diol core influences the mode of binding to the active site aspartic acids. Diastereomers with similar binding affinity can bind in different, asym. and sym., modes, while those with different binding affinities can bind in a similar manner. The positional symmetry of an inhibitor with respect to the enzyme C2 axis may be distinguished from its conformational symmetry. The structural differences between the inhibitor complexes were mainly confined to the central core portion of the diols, can be described by torsional differences about the central three bonds, and primarily affect interactions within the active site pocket formed by Asp 25/125 and Gly 27/127. Some flexibility in the enzyme backbone at Gly 127 was also apparent. Based on these results, the authors suggest that the binding mode for central hydroxy-bearing, C2-sym. inhibitors will be detd. by how well the inhibitor can simultaneously optimize hydrogen bonding with the active site carboxylate groups and van der Waals contacts with the neighboring backbone atoms of the active site ".psi."-loops. A sym. hydrogen-bonding arrangement with either one or two sym. positioned hydroxy groups appears to be preferred over less sym. configurations.

IT 134805-77-9, A 76889 134878-16-3, A 76928  
134878-17-4, A 77003 144141-70-8, A 78791  
RL: BIOL (Biological study)

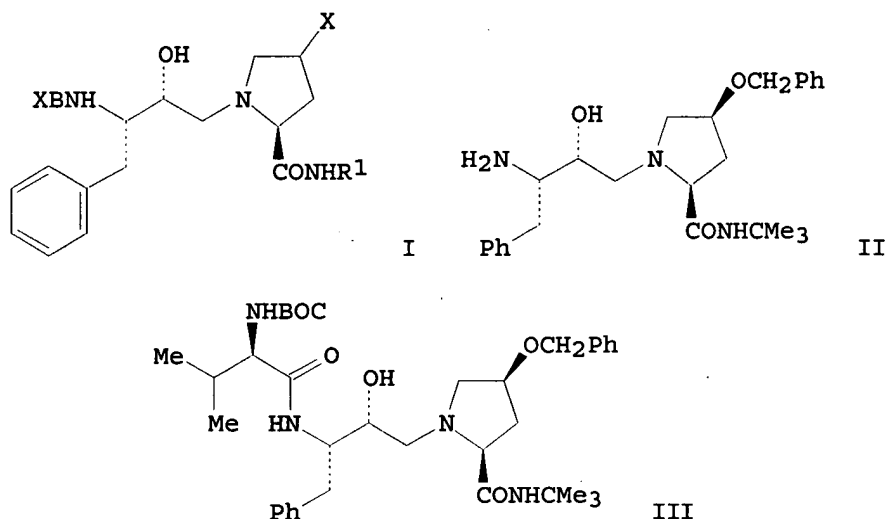
(HIV-1 Proteinase inhibition by,  
structure in, antiviral activity relation to)

L9 ANSWER 53 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1994:135132 CAPLUS  
 DN 120:135132  
 TI Substituted pyrrolidine derivatives as HIV protease inhibitors  
 IN Gorys, Vida; Soucy, Francois; Yoakim, Christiane; Beaulieu, Pierre  
 Louis  
 PA Bio-Mega/Boehringer Ingelheim Research Inc., Can.  
 SO Eur. Pat. Appl., 26 pp.  
 CODEN: EPXXDW

DT Patent  
 LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	EP 560269	A1	19930915	EP 93-103713	19930309
	EP 560269	B1	19950531		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	ZA 9301777	A	19930923	ZA 93-1777	19930212
	CA 2092653	AA	19930914	CA 93-2092653	19930312
	AU 9335165	A1	19930916	AU 93-35165	19930312
	AU 663164	B2	19950928		
	HU 70147	A2	19950928	HU 93-729	19930312
	PL 173459	B1	19980331	PL 93-298038	19930312
	JP 06025158	A2	19940201	JP 93-54141	19930315
	CN 1096292	A	19941214	CN 93-106800	19930608
	US 5552405	A	19960903	US 95-509268	19950731
PRAI	US 92-850596		19920313		
	US 93-25681		19930303		
	US 94-198237		19940218		
	US 94-326442		19941020		
OS	MARPAT 120:135132				
GI					



AB The title compds., (S)-pyrrolidine-2-carboxamides I (X = acyl, alkoxycarbonyl, etc.; B = bond, aminocarbonyl linkage, etc.; R1 = alkyl, cycloalkyl; Y = acyl, alkylsulfonyl, etc.) and their uses for the treatment of HIV infections in humans (virucides) is claimed. A process for the prepn. of I comprises a ring opening reaction of an epoxide deriv. with an (S)-2-pyrrolidinecarboxamide deriv. For example, coupling of a valine deriv. with protected 1-[3(S)-amino-2(R)-hydroxy-4-phenylbutyl]-4(S)-benzyloxy-2(S)-pyrrolidinecarboxamide (II) gave 4(S)-benzyloxy-1-[3(S)-[N-(benzyloxycarbonyl)valyl]amino]-2(R)-hydroxy-4-phenylbutyl]-2(S)-pyrrolidinecarboxamide III. The in vitro inhibitory concn. for HIV protease for III was 150 nM.

IT 152892-87-0P 152892-89-2P 152892-90-5P  
152892-95-0P 152892-99-4P 152893-00-0P  
152893-01-1P 152893-02-2P 152893-05-5P  
152983-98-7P 152984-00-4P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, as HIV protease inhibitor  
(virucide))

L9 ANSWER 54 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1994:107712 CAPLUS

DN 120:107712

TI The synthesis of novel HIV-protease inhibitors via silica gel assisted addition of amines to epoxides

AU Bennett, Frank; Patel, Naginbhai M.; Girijavallabhan, Viyyoor M.; Ganguly, Ashit K.

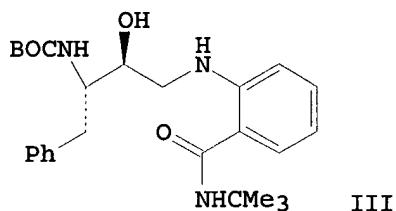
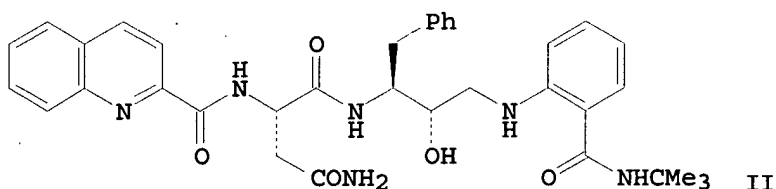
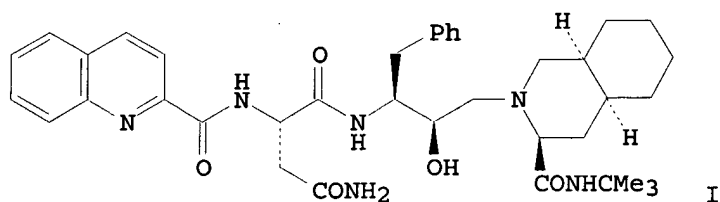
CS Schering-Plough Res. Inst., Kenilworth, NJ, 07033, USA

SO Synlett (1993), (9), 703-4

Searcher : Shears 308-4994

CODEN: SYNLES; ISSN: 0936-5214

DT Journal  
 LA English  
 OS CASREACT 120:107712  
 GI



AB HIV-protease inhibitors, contg. novel .beta.-hydroxy secondary amine transition state isosteres, are constructed using a silica gel mediated addn. of unreactive amines to epoxides as the key step. Virally encoded aspartic protease from HIV-1 is a target for chemotherapeutic intervention of AIDS. Blocking of this enzyme results in termination of post-translational processing of viral gag and gag-pol polyprotein gene products and prodn. of non-infectious virions. An analog of the known .beta.-hydroxy ethylamine transition state dipeptide isostere I which carry simplified arom. hydrophobic ligands, i.e. the compd. II, was prepd. A key step in the synthetic sequence was the silica gel-mediated aminolysis of epoxides with anthranilate derivs. to give intermediates, such as III.

IT 127779-20-8P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

Searcher : Shears 308-4994

(prepn. of, as HIV protease inhibitor  
)

L9 ANSWER 55 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1994:94796 CAPLUS  
 DN 120:94796  
 TI Peptide mimetics as enzyme inhibitors: Use of free energy  
 perturbation calculations to evaluate isosteric replacement for  
 amide bonds in a potent HIV protease inhibitor  
 AU Cieplak, Piotr; Kollman, Peter A.  
 CS Dep. Pharm. Chem., Univ. California, San Francisco, CA, 94143, USA  
 SO J. Comput.-Aided Mol. Des. (1993), 7(3), 291-304  
 CODEN: JCADEQ; ISSN: 0920-654X  
 DT Journal  
 LA English  
 AB The authors present the application of free energy perturbation  
 theory/mol. dynamics to predict the consequence of replacing each of  
 the seven peptide bonds in the potent HIV protease inhibitor JG365:  
 ACE (acetyl)-Ser-Leu-Asn-HEA (hydroxyethylamine analog of  
 Phe-Pro)-Ile-Val-NME (N-methyl) by ethylene or fluoroethylene  
 isosteres. Replacing two of these bonds may well lead to  
 significantly tighter binding; replacing two others is predicted to  
 significantly diminish the binding affinity. Also, for three of the  
 peptide bonds fluoroethylene replacements could lead to increased  
 binding of free energies of the inhibitors. The authors' results  
 should be considered as predictive since there are, as yet, no  
 exptl. results on such peptide replacements as enzyme inhibitors.  
 IT 132748-20-0, JG 365  
 RL: BIOL (Biological study)  
 (protease inhibition by, in HIV,  
 QSAR of)

L9 ANSWER 56 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1994:94447 CAPLUS  
 DN 120:94447  
 TI Design and structure of symmetry-based inhibitors of HIV-1 protease  
 AU Erickson, John W.  
 CS Struct. Biochem. Program, PRI/Dyn Corp., Frederick, MD, 21702, USA  
 SO Perspect. Drug Discovery Des. (1993), 1(1), 109-28  
 CODEN: PDDDEC  
 DT Journal; General Review  
 LA English  
 AB A review with 50 refs. on the design of novel series of  
 C2-symmetry-based inhibitors of HIV-1 protease.  
 IT 152886-86-7D, derivs.  
 RL: BIOL (Biological study)  
 (as HIV-1 protease inhibitors,  
 against HIV-1, for treatment of AIDS, in humans, structure in  
 relation to)

L9 ANSWER 57 OF 82 CAPLUS COPYRIGHT 1999 ACS  
AN 1994:68731 CAPLUS  
DN 120:68731  
TI Inactivation of a yeast transactivator by the fused HIV-1  
proteinase: A simple assay for inhibitors of the viral enzyme  
activity  
AU Murray, Michael G.; Hung, Wesley; Sadowski, Ivan; Das Mahapatra,  
Bimalendu  
CS Schering-Plough Res. Inst., Kenilworth, NJ, 07033-0539, USA  
SO Gene (1993), 134(1), 123-8  
CODEN: GENED6; ISSN: 0378-1119  
DT Journal  
LA English  
AB The human immunodeficiency virus type 1 (HIV-1) proteinase (PR) and  
its flanking sequences have been fused in frame between the  
DNA-binding domain and the transcription-activation domain of the  
yeast protein, GAL4. As has been shown before with the 3C  
proteinase of Cocksackie virus B3 (CVB3), the GAL4::PR fusion protein  
retains its GAL4 function, providing the PR is inactive. When PR is  
active, its autocatalytic activity in the hybrid protein is shown to  
inactivate the transactivation function of GAL4. This provides a  
simple assay to monitor PR activity. A dose-dependent effect of a  
potent PR-specific inhibitor (SCH 52852) is demonstrated in this  
system and illustrates the sensitivity of the assay. The assay is  
used for high throughput screening to identify novel inhibitors of  
the viral PR, and provides a method to generate and analyze mutants  
and revertants of the PR.  
IT 127779-20-8, Sch 52852  
RL: ANST (Analytical study)  
(HIV-1 proteinase inhibition by,  
fusion product with yeast GAL4 protein in assay of)

L9 ANSWER 58 OF 82 CAPLUS COPYRIGHT 1999 ACS  
AN 1993:603375 CAPLUS  
DN 119:203375  
TI Potent HIV protease inhibitors: the development of  
tetrahydrofuranylglycines as novel P2-ligands and pyrazine amides as  
P3-ligands  
AU Ghosh, Arun K.; Thompson, Wayne J.; Holloway, M. Katharine; McKee,  
Sean P.; Duong, Tien T.; Lee, Hee Yoon; Munson, Peter M.; Smith,  
Anthony M.; Wai, Jenny M.; et al.  
CS Dep. Med. Chem., Merck Res. Lab., West Point, PA, 19486, USA  
SO J. Med. Chem. (1993), 36(16), 2300-10  
CODEN: JMCMAR; ISSN: 0022-2623  
DT Journal  
LA English  
OS CASREACT 119:203375; CJACS  
GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB A series of protease inhibitors bearing constrained unnatural amino acids at the P2-position and novel heterocycles at the P3-position of compd. I (R = R1; Ro 31-8959) were synthesized, and their in vitro enzyme inhibitory and antiviral activities were evaluated. Replacement of P2-asparagine of compd. I (R = R1) with (2S,3'R)-tetrahydrofuranylglycine resulted in improvement in enzyme inhibitory as well as antiviral potencies (compd. I; R = R2). Interestingly, incorporation of (2S,3'S)-tetrahydrofuranylglycine at the P2-position proved to be less effective. The resulting compd. I (R = R3) was 100-fold less potent than the 2S,3R-isomer (compd. I; R = R2). This stereochem. preference indicated a hydrogen-bonding interaction between the tetrahydrofuranyl oxygen and the residues of the S2-region of the enzyme active site. Furthermore, replacement of P3-quinolinoyl ligand of I (R = R1) with various novel heterocycles resulted in potent inhibitors of HIV proteases. Of particular interest, compd. I (R = R4) with (2S,3'R)-tetrahydrofuranylglycine at P2 and pyrazine deriv. at P3 is one of the most potent inhibitors of HIV-1 (IC50 value 0.07 nM) and HIV-2 (IC50 value 0.18 nM) proteases. Another important result in this series is the identification of compd. I (R = R5) in which the P2-P3-amide carbonyl has been removed. The resulting compd. I (R = R5) has exhibited improvement in antiviral potency while retaining the enzyme inhibitory potency similar to compd. I (R = R1).

IT 127779-20-8DP, analogs 146255-24-5P

146278-31-1P 150331-78-5P 150331-82-1P  
150331-83-2P 150331-84-3P 150331-88-7P  
150331-89-8P 150331-90-1P 150331-91-2P  
150331-92-3P 150331-93-4P 150331-94-5P  
150331-95-6P 150331-96-7P 150406-29-4P

RL: BAC (Biological activity or effector, except adverse); SPN  
(Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(prepn., HIV-1 protease inhibition  
and antiviral activity of)

IT 150331-87-6P 150406-28-3P

RL: BAC (Biological activity or effector, except adverse); SPN  
(Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(prepn., S-oxidn., HIV-1 protease  
inhibition and antiviral activity of)

L9 ANSWER 59 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1993:603319 CAPLUS

DN 119:203319

TI Preparation of decahydroisoquinolinecarboxamides as HIV protease

Searcher : Shears 308-4994



## inhibitors

IN Thompson, Wayne J.; Ghosh, Arun K.; Lee, Hee Yoon; Huff, Joel R.

PA Merck and Co., Inc., USA

SO Eur. Pat. Appl., 30 pp.

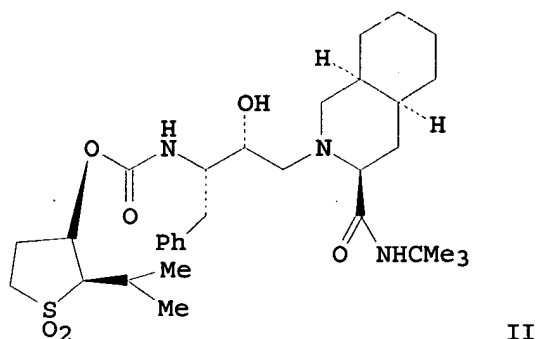
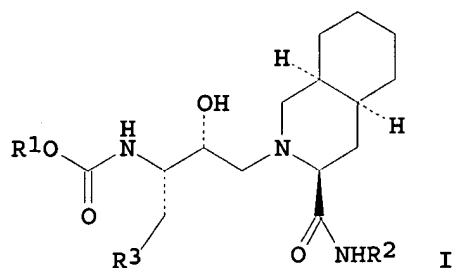
CODEN: EPXXDW

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 539192	A1	19930428	EP 92-309639	19921021
	EP 539192	B1	19990107		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	WO 9308184	A1	19930429	WO 92-US8758	19921014
	W: BG, CS, FI, HU, KR, NO, PL, RO, RU				
	CA 2081134	AA	19930424	CA 92-2081134	19921022
	AU 9227253	A1	19930429	AU 92-27253	19921022
	AU 649170	B2	19940512		
	ZA 9208164	A	19930503	ZA 92-8164	19921022
	JP 05239031	A2	19930917	JP 92-309474	19921023
	JP 06078314	B4	19941005		
	US 5502060	A	19960326	US 94-328936	19941025
PRAI	US 91-781470		19911023		
	US 92-929991		19920821		
	US 93-144094		19931027		
OS	MARPAT 119:203319				
GI					



AB Title compds. [I; R1 = (unsatd.) (substituted) 5-7 membered carbocyclyl, heterocyclyl; R2 = (substituted) alkyl, (substituted) (unsatd.) 5-7 membered carbocyclyl; R3 = (substituted) Ph, cycloalkyl], were prepd. Thus, 2(R,S)-methylethyl-3(R,S)-tetrahydrothienyl 2-pyridyl carbonate (prepn. given) and N-tert-Bu decahydro-2-(2R-hydroxy-4-phenyl-3S-aminobutyl)-(4aS,8aS)-isoquinoline-3S-carboxamide (prepn. given) were stirred with Et3N in CH2Cl2 to give the diamide, which was S-oxidized with N-methylmorpholine oxide/OsO4 in actone/H2O/Me3COH to give, after chromatog., title compd. II. II inhibited HIV protease with IC50 = 4 nM.

IT 145631-02-3P 145631-07-8P 145631-08-9P  
 145680-05-3P 145680-06-4P 146611-25-8P  
 147949-29-9P 147949-30-2P 147977-17-1P  
 147977-21-7P 150330-55-5P 150330-56-6P  
 150330-57-7P 150330-58-8P 150330-59-9P  
 150330-60-2P 150330-61-3P 150330-62-4P  
 150330-63-5P 150330-64-6P 150330-65-7P  
 150330-66-8P 150330-67-9P 150406-19-2P  
 150406-20-5P 150406-21-6P 150406-22-7P  
 150406-23-8P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of, as HIV protease inhibitor

Searcher : Shears 308-4994

)

L9 ANSWER 60 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1993:485387 CAPLUS  
 DN 119:85387  
 TI A symmetric inhibitor binds HIV-1 protease asymmetrically  
 AU Dreyer, Geoffrey B.; Boehm, Jeffrey C.; Chenera, Balan; DesJarlais, Renee L.; Hassell, Anne M.; Meek, Thomas D.; Tomaszek, Thaddeus A., Jr.; Lewis, Mitchell  
 CS Dep. Med. Chem., SmithKline Beecham Pharm., King of Prussia, PA, 19406, USA  
 SO Biochemistry (1993), 32(3), 937-47  
 CODEN: BICHAW; ISSN: 0006-2960  
 DT Journal  
 LA English  
 OS CJACS  
 AB Potential advantages of C2-sym. inhibitors designed for the sym. HIV-1 protease include high selectivity, potency, stability, and bioavailability. Pseudo-C2-sym. monools and C2-sym. diols, contg. central hydroxymethyl and (R,R)-dihydroxyethyl moieties flanked by a variety of hydrophobic P1/P1' side chains, were studied as HIV-1 protease inhibitors. The monools and diols were synthesized in 8-10 steps from D-(+)-arabitol and D-(+)-mannitol, resp. Monools with Et or iso-Bu P1/P1' side chains were weak inhibitors of recombinant HIV-1 protease ( $K_i > 10 \mu\text{M}$ ), while benzyl P1/P1' side chains afforded a moderately potent inhibitor (apparent  $K_i = 230 \text{ nM}$ ). Diols were 100-10 000.times. more potent than analogous monools, and a wider range of P1/P1' side chains led to potent inhibition. Both classes of compds. exhibited lower apparent  $K_i$  values under high-salt conditions. Surprisingly, monool and diol HIV-1 protease inhibitors were potent inhibitors of porcine pepsin, a prototypical asym. monomeric aspartic protease. These results were evaluated in the context of the pseudosym. structure of monomeric aspartic proteases and their evolutionary kinship with the retroviral proteases. The X-ray crystal structure of HIV-1 protease complexed with a sym. diol was detd. at 2.6 .ANG.. Contrary of expectations, the diol binds the protease asym. and exhibits 2-fold disorder in the electron d. map. Mol. dynamics simulations were conducted beginning with asym. and sym. HIV-1 protease/inhibitor mode complexes. A more stable trajectory resulted from the asym. complex, in agreement with the obsd. asym. binding mode. A simple four-point model was used to argue more generally that van der Waals and electrostatic force fields can commonly lead to an asym. assocn. between sym. mols.

IT 129467-48-7P 142285-33-4P 142285-35-6P  
 142285-39-0P 142285-40-3P 142285-41-4P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. and HIV-1 protease inhibition  
 by, structure in relation to)

Searcher : Shears 308-4994

L9 ANSWER 61 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1993:409161 CAPLUS  
 DN 119:9161  
 TI HIV protease inhibitors  
 IN Mimoto, Tsutomu; Hattori, Naoko; Nagano, Yuuichi; Shintani, Makoto;  
 Kiso, Yoshiaki  
 PA Nippon Mining Co., Ltd., Japan  
 SO Eur. Pat. Appl., 86 pp.  
 CODEN: EPXXDW  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 490667	A2	19920617	EP 91-311549	19911211
	EP 490667	A3	19930505		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	CA 2056911	AA	19920612	CA 91-2056911	19911204
	JP 05170722	A2	19930709	JP 91-348705	19911205
	JP 2700511	B2	19980121		
	AU 9188900	A1	19920618	AU 91-88900	19911206
	AU 653972	B2	19941020		
	ZA 9109721	A	19921230	ZA 91-9721	19911210
	FI 9105819	A	19920612	FI 91-5819	19911211
	NO 9200023	A	19920727	NO 92-23	19920102

PRAI JP 90-409673 19901211  
 JP 91-25755 19910125  
 JP 91-89976 19910328  
 JP 91-169174 19910614  
 JP 91-304043 19911023

OS MARPAT 119:9161

AB A-B1-B2-B3-NHCHR1CH(OH)CO-B4-B5-B6-XR2R3 [A = H, N-protecting group;  
 B1-B6 = (un)substituted amino acid residue, bond; R1 =  
 (un)substituted alkyl, cycloalkyl, aryl, heterocyclic; R2, R3 = H  
 (un)substituted hydrocarbon; X = N, O; R3 absent if X = O] (188  
 compds.) were prepd. Thus, PhCH2CH2CO-Asn-X1-Pro-Ile-Val-NH2 [X1 =  
 (2R,3S)-NHCH(CH2Ph)CH(OH)CO, I] was prepd. by solid-phase synthesis.  
 HIV protease treated with 1mM I showed 1.5% residual activity.

IT 138228-18-9P 138228-19-0P 138228-20-3P  
 138228-21-4P 138258-64-7P 139694-65-8P  
 139694-67-0P 139757-45-2P 139758-09-1P  
 139758-10-4P 139758-11-5P 139758-12-6P  
 141171-77-9P 141171-80-4P 143909-13-1P  
 143909-14-2P 143909-15-3P 143909-16-4P  
 143909-18-6P 143909-19-7P 143909-20-0P  
 143909-21-1P 143909-22-2P 143909-23-3P  
 143909-24-4P 143909-25-5P 143909-26-6P  
 143909-28-8P 143909-29-9P 143909-30-2P

Searcher : Shears 308-4994

143909-31-3P 143909-35-7P 143909-36-8P  
 143934-16-1P 143934-17-2P 143934-18-3P  
 143934-19-4P 143934-20-7P 143934-21-8P  
 143934-22-9P 143934-23-0P 143934-24-1P  
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 143935-32-4P 143935-33-5P 143935-34-6P  
 143935-35-7P 143935-36-8P 143957-41-9P  
 143957-42-0P 144016-87-5P 147657-50-9P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. and HIV protease-inhibiting  
 activity of)

IT 143935-56-2P 143935-61-9P 143978-14-7P  
 143978-16-9P 143978-18-1P 143978-23-8P  
 143978-33-0P 143978-38-5P 143978-39-6P  
 143978-54-5P 143978-61-4P 143978-67-0P  
 143978-68-1P 143978-70-5P 143978-71-6P  
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 143978-81-8P 143978-83-0P 143978-84-1P  
 143979-32-2P 143979-42-4P 143979-43-5P  
 143979-46-8P 143979-48-0P 143979-51-5P  
 143979-55-9P 143979-56-0P 144005-44-7P  
 144069-69-2P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn., deblocking, and HIV protease-  
 inhibiting peptide synthesis with)

L9 ANSWER 62 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1993:409149 CAPLUS

DN 119:9149

TI NMR studies of four isomers of decahydroisoquinoline-3(S)-carboxylic acid and a potent HIV proteinase inhibitor incorporating the (S,S,S) isomer

AU Gilbert, Jenny C.; Redshaw, Sally; Simmonite, Heather S.; Thomas, W. Anthony; Whitcombe, Ian W. A.

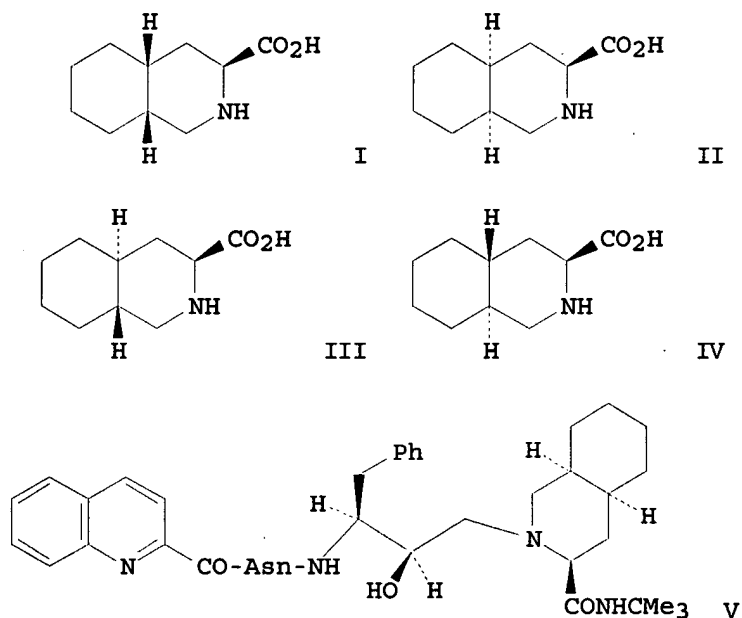
CS Roche Prod. Ltd., Welwyn Garden City/Herts., AL7 3AY, UK

SO J. Chem. Soc., Perkin Trans. 2 (1993), (3), 475-9

Searcher : Shears 308-4994

CODEN: JCPKBH; ISSN: 0300-9580

DT Journal  
 LA English  
 GI



AB The stereochem. and conformations of decahydroisoquinoline-3(S)-carboxylic acid (DHIQ) stereoisomers I-IV have been elucidated by NMR spectroscopy. A potent HIV proteinase inhibitor, Ro 31-8959 (V), incorporating the (S,S,S)-isomer of DHIQ, has also been examd. and crit. conformational features compared with those found in the x-ray structure of the enzyme-bound inhibitor.

IT 128053-46-3 147922-51-8 147922-52-9

RL: RCT (Reactant)

(HIV proteinase-inhibiting activity of)

IT 127779-20-8

RL: RCT (Reactant)

(conformation and HIV proteinase-inhibiting activity of)

L9 ANSWER 63 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1993:408656 CAPLUS

DN 119:8656

TI Cyclic sulfolanones as novel and high-affinity P2 ligands for HIV-1 protease inhibitors

AU Ghosh, Arun K.; Thompson, Wayne J.; Lee, Hee Yoon; McKee, Sean P.;  
 Searcher : Shears 308-4994

Munson, Peter M.; Duong, Tien T.; Darke, Paul L.; Zugay, Joan A.; Emini, Emilio A.; et al.

CS Dep. Med. Chem., Mol. Biol., Merck Res. Lab., West Point, PA, 19486, USA

SO J. Med. Chem. (1993), 36(7), 924-7

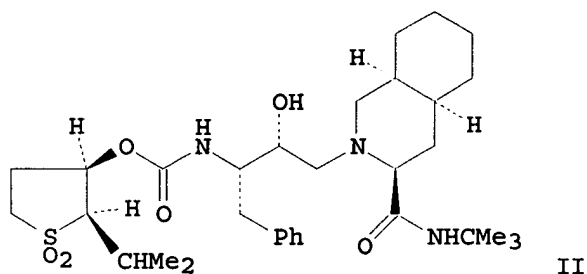
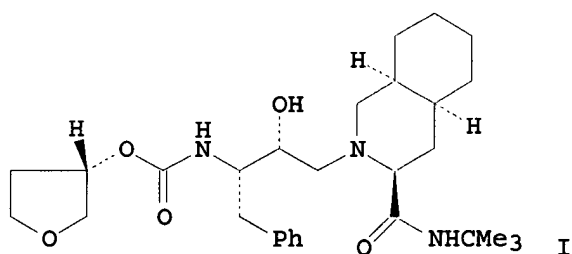
CODEN: JMCMAR; ISSN: 0022-2623

DT Journal

LA English

OS CASREACT 119:8656; CJACS

GI



AB Recently the use of urethanes of 3-tetrahydrofuran as P2-ligands for the S2-substrate binding site of HIV-1 protease was reported. The urethane of (S)-3-hydroxy sulfolane substantially increased the in vitro potency of inhibitors relative to the heterocycle 3-tetrahydrofuran. Furthermore, introduction of a small 2-alkyl group cis to the 3-hydroxyl group of either heterocycle system further enhances enzyme affinity. This is consistent with modeling studies using the x-ray crystal structure of the enzyme-inhibitor complex of THF derived inhibitor I and HIV-1 protease. The cis-2-iso-Pr group thus far offers optimum enhancement of the inhibitory properties of the 3-hydroxysulfolane providing an inhibitor II; for HIV-1, IC50 3 nM; for HIV-219, IC50 17 nM) of comparable in vitro antiviral potency to present clin. candidate (3S,4aS,8aS,2'R,3'S)-N-tert-butyl-2-(2'-hydroxy-4'-phenyl-3'-[[[N-(2-

Searcher : Shears 308-4994

quinolinylcarbonyl)-L-asparaginyll]amino]butyl]-decahydroisoquinoline-3-carboxamide (Ro 31-8959), but of reduced mol. wt. due to the exclusion of the P3-quinoline ligand. A stereoselective and general synthetic route to this novel class of ligands in optically pure form was developed.

IT 145631-07-8 147949-30-2 147949-31-3  
147949-32-4 147949-33-5 147949-34-6  
147949-35-7 147977-17-1 147977-18-2  
147977-19-3 147977-20-6 147977-21-7  
147977-22-8

RL: RCT (Reactant)

(HIV protease inhibitor)

IT 147949-29-9P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(prepn. of, as HIV protease inhibitor  
)

L9 ANSWER 64 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1993:234430 CAPLUS

DN 118:234430

TI Symmetry-based inhibitors of HIV protease. Structure-activity studies of acylated 2,4-diamino-1,5-diphenyl-3-hydroxypentane and 2,5-diamino-1,6-diphenylhexane-3,4-diol

AU Kempf, Dale J.; Codacovi, Lynnmarie; Wang, Xiu Chun; Kohlbrenner, William E.; Wideburg, Norman E.; Saldivar, Ayda; Vasavanonda, Sudthida; Marsh, Kennan C.; Bryant, Pamela; et al.

CS Pharm. Prod. Div., Abbott Lab., Abbott Park, IL, 60064, USA

SO J. Med. Chem. (1993), 36(3), 320-30

CODEN: JMCMAR; ISSN: 0022-2623

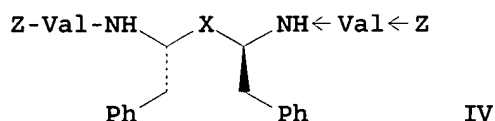
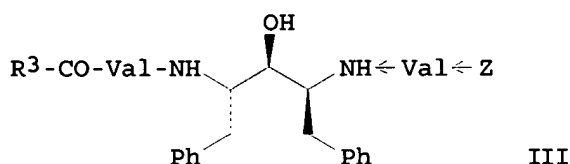
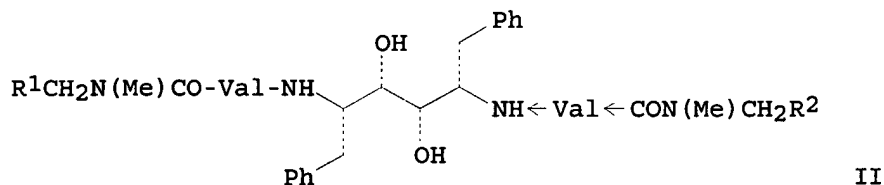
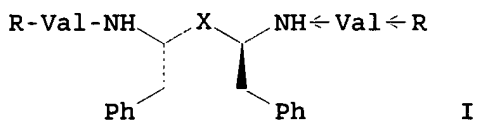
DT Journal

LA English

OS CJACS

GI





AB Title sym. substituted compds. I [R = (2-pyridylmethoxy)carbonyl, [2-(4-morpholinyl)ethoxy]carbonyl, trans-3-(2-pyridyl)acryloyl, (2-pyridylmethyl)methylamino]carbonyl, [(2-pyridylmethyl)methylamino]sulfonyl, etc.; X = (R,R)-CH(OH)CH(OH), (R,S)-CH(OH)CH(OH), (S,S)-CH(OH)CH(OH), CH(OH)] were prepd. as inhibitors of human immunodeficiency virus (HIV) protease, the enzyme responsible for maturation of HIV. Unsym. substituted HIV protease inhibitors II (R1 = 2-pyridyl, R2 = 3-pyridyl, 4-thiazolyl, 2-thiazolyl; R1 = 2-pyridyl, 2-thiazolyl, 4-thiazolyl, R2 = 2-aminothiazol-4-yl) and unsym. substituted mono-ol inhibitors III [Z = benzyloxycarbonyl; R3 = PhCH2O, 2-pyridylmethoxy, 3-pyridylmethoxy, 4-pyridylmethoxy, (1-methyl-3-piperidinyl)methoxy, (1-methyl-2-piperidinyl)methoxy, 2-(4-morphinyl)ethoxy, 2-(1-pyrrolidinyl)ethoxy, 4-methyl-1-piperazinyl] were also prepd. Structure-activity relationships were studied. Beginning with lead compds. IV, the effect of adding polar, heterocyclic end groups to one or both ends of the sym. or pseudosym. inhibitors was probed. Aq. soly. was enhanced > 1000-fold while maintaining potent inhibition of purified HIV-1 protease and anti-HIV activity in vitro. Pharmacokinetic studies in rats indicated a substantial difference in the absorption properties of mono-ol-based and diol-based inhibitors. The oral bioavailability of inhibitor I [R = (2-pyridylmethoxy)carbonyl, X = CH(OH)] in rats was 19%; however, the Cmax obtained failed to exceed the anti-HIV EC50 in vitro.

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Substantial plasma levels of potent inhibitors of the diol class were not obtained after oral administration in rats; however, the optimal combination of aq. soly. and in vitro antiviral activity of several inhibitors support their potential use in i.v. therapy.

IT 134805-69-9P 134805-76-8P 134805-77-9P  
 134805-80-4P 134805-82-6P 134805-85-9P  
 134805-89-3P 134878-09-4P 134878-10-7P  
 134878-11-8P 134878-16-3P 134878-17-4P  
 134878-18-5P 134878-19-6P 134878-20-9P  
 134878-21-0P 137828-39-8P 144141-71-9P  
 144141-75-3P 144141-77-5P 144142-36-9P  
 144142-38-1P 144142-39-2P 144142-45-0P  
 144142-46-1P 144142-47-2P 144142-57-4P  
 144142-58-5P 144142-60-9P 144142-61-0P  
 144142-63-2P 144142-64-3P 144154-80-3P  
 144154-81-4P 144162-21-0P 144162-22-1P  
 144162-38-9P 144179-89-5P 144179-94-2P  
 144179-98-6P 144179-99-7P 144180-00-7P  
 144239-35-0P 144239-36-1P 144239-37-2P  
 144239-40-7P 144239-41-8P 144239-42-9P  
 144239-43-0P 147146-07-4P 147146-10-9P  
 147201-57-8P 147201-58-9P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. and HIV protease-inhibiting  
 activity of)

L9 ANSWER 65 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1993:204690 CAPLUS  
 DN 118:204690  
 TI Kynostatin (KNI)-227 and -272, highly potent anti-HIV agents:  
 conformationally constrained tripeptide inhibitors of HIV protease  
 containing allophenylnorstatine  
 AU Mimoto, Tsutomu; Imai, Junya; Kisanuki, Sumitsugu; Enomoto, Hiroshi;  
 Hattori, Naoko; Akaji, Kenichi; Kiso, Yoshiaki  
 CS Dep. Med. Chem., Kyoto Pharm. Univ., Kyoto, 607, Japan  
 SO Chem. Pharm. Bull. (1992), 40(8), 2251-3  
 CODEN: CPBTAL; ISSN: 0009-2363  
 DT Journal  
 LA English  
 AB Selective and potent HIV protease inhibitors contg.  
 allophenylnorstatine [Apns; (2S,3S)-3-amino-2-hydroxy-4-  
 phenylbutyric acid] as a transition-state mimic were designed and  
 synthesized. Among them, conformationally constrained tripeptide  
 derivs., kynostatin (KNI)-227 and -272 exhibited highly potent  
 antiviral activities against a wide spectrum of HIV isolates. Ready  
 availability due to the simple synthetic procedure and the excellent  
 antiviral properties indicate that KNI-227 and KNI-272 are promising  
 candidates as selective anti-AIDS drugs.  
 IT 139694-65-8 141171-77-9, KNI 144  
 Searcher : Shears 308-4994

141171-80-4 143934-32-1 143934-35-4  
 143934-36-5 143934-41-2 143934-43-4  
 147384-71-2

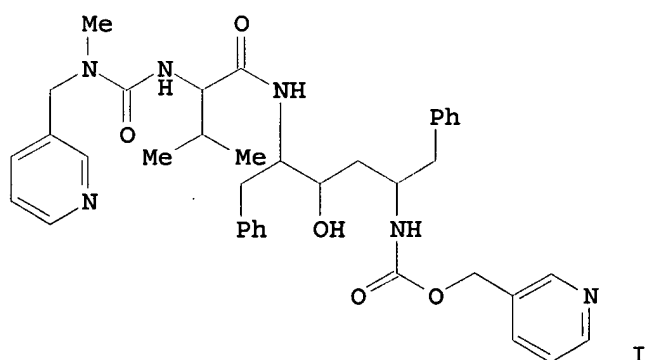
RL: BIOL (Biological study)  
 (HIV protease inhibiting activity  
 of, structure in relation to)

L9 ANSWER 66 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1993:192283 CAPLUS  
 DN 118:192283  
 TI amino acid derivatives as HIV-1 protease inhibitors and methods for  
 their synthesis  
 IN Kempf, Dale J.; Codacovi, Lynn M.; Norbeck, Daniel W.; Plattner,  
 Jacob J.; Sham, Hing L.; Wittenberger, Steven J.; Zhao, Chen  
 PA Abbott Laboratories, USA  
 SO Eur. Pat. Appl., 154 pp.  
 CODEN: EPXXDW  
 DT Patent  
 LA English  
 FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	EP 486948	A2	19920527	EP 91-119464	19911104
	EP 486948	A3	19930825		
	R: AT, BE, DE, DK, FR, GB, GR, LU, NL, SE				
	AU 9187715	A1	19920521	AU 91-87715	19911108
	AU 650491	B2	19940623		
	CA 2055670	AA	19920521	CA 91-2055670	19911115
	CH 684696	A	19941130	CH 91-3384	19911119
	CH 688551	A	19971114	CH 94-3618	19911119
	CH 689001	A	19980715	CH 97-2338	19911119
	JP 04308574	A2	19921030	JP 91-354231	19911120
	ES 2070660	A1	19950601	ES 91-2579	19911120
	ES 2070660	B1	19960101		
	US 5354866	A	19941011	US 93-121673	19930914
	US 5541334	A	19960730	US 95-409380	19950323
	US 5597926	A	19970128	US 95-409767	19950323
	US 5616714	A	19970401	US 95-410260	19950324
	US 5648497	A	19970715	US 95-410623	19950324
	US 5837873	A	19981117	US 95-410162	19950324
	US 5539122	A	19960723	US 95-410996	19950327
	US 5552558	A	19960903	US 95-411032	19950327
	US 5696270	A	19971209	US 95-411140	19950327
	US 5580984	A	19961203	US 95-412253	19950328
	US 5679797	A	19971021	US 95-412244	19950328
	US 5583232	A	19961210	US 95-412821	19950329
	US 5597927	A	19970128	US 95-412438	19950329
	US 5674882	A	19971007	US 95-413136	19950329
	US 5583233	A	19961210	US 95-413290	19950330

Searcher : Shears 308-4994

US 5625072	A	19970429	US 95-415827	19950403
US 5591860	A	19970107	US 95-416272	19950404
US 5597928	A	19970128	US 95-416607	19950404
US 5608072	A	19970304	US 95-416259	19950404
US 5565418	A	19961015	US 95-417304	19950405
US 5659044	A	19970819	US 95-417165	19950405
US 5659045	A	19970819	US 95-417295	19950405
US 5616720	A	19970401	US 95-418056	19950406
US 5635523	A	19970603	US 95-417879	19950406
US 5554783	A	19960910	US 95-418978	19950407
US 5541206	A	19960730	US 95-423387	19950425
PRAI US 90-616170		19901120		
US 91-746020		19910815		
US 91-777626		19911023		
US 94-270210		19940823		
US 83-355945		19830523		
US 89-355945		19890523		
US 89-405604		19890908		
US 89-456124		19891222		
US 90-518730		19900509		
US 92-998114		19921229		
US 93-121673		19930914		
US 93-158587		19931202		
OS	CASREACT 118:192283; MARPAT 118:192283			
GI				



AB Certain 2-alkoxy-1,4-butanediamine derivs. are claimed. Specific compds. such as (2S,3S,5S)-2-[N-[N-[N-methyl-N-[(2-pyridyl)methyl]amino]carbonyl]valinyl]amino]-5-[N-[(3-pyridinyl)methoxycarbonyl]amino]-1,6-diphenyl-3-hydroxyhexane I, their salts, and prodrug forms thereof are claimed. The use of such compds. for the manuf. of pharmaceuticals for the treatment of HIV

Searcher : Shears 308-4994

infections and their use for the inhibition of HIV protease are claimed. I in vivo was an HIV-1 protease inhibitor and it was active against HIV-13b.

IT 137649-69-5 144163-85-9 144163-90-6  
144186-45-8 144239-97-4

RL: RCT (Reactant)

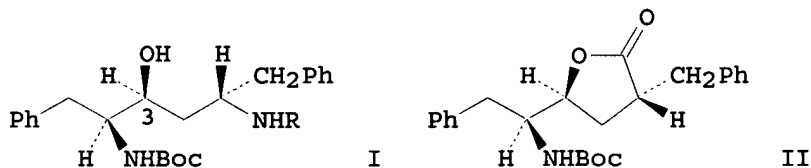
(intermediate for HIV protease  
inhibitor)

IT 144141-68-4P 144141-69-5P 144141-70-8P  
144141-71-9P 144141-75-3P 144141-76-4P  
144141-77-5P 144141-78-6P 144141-79-7P  
144141-82-2P 144141-83-3P 144141-84-4P  
144141-85-5P 144141-86-6P 144141-90-2P  
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RL: BAC (Biological activity or effector, except adverse); SPN  
 (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (prepn. of, as HIV-1 protease  
 inhibitor)

L9 ANSWER 67 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1993:169576 CAPLUS  
 DN 118:169576  
 TI Potent HIV-1 protease inhibitors: stereoselective synthesis of a  
 dipeptide mimic  
 AU Ghosh, Arun K.; McKee, Sean P.; Thompson, Wayne J.; Darke, Paul L.;  
 Zugay, Joan C.  
 CS Dep. Med. Chem. Mol. Biol., Merck Res. Lab., West Point, PA, 19486,  
 USA  
 SO J. Org. Chem. (1993), 58(5), 1025-9  
 CODEN: JOCEAH; ISSN: 0022-3263  
 DT Journal  
 LA English  
 OS CASREACT 118:169576; CJACS  
 GI



AB The synthesis of a differentially protected dipeptide mimic I (R =  
 CO<sub>2</sub>CH<sub>2</sub>Ph, Boc = CO<sub>2</sub>CMe<sub>3</sub>) in enantiomerically pure form is described.  
 The key step involves the epimerization of the C-2 center of the  
 lactone II, hydrolysis and protection of the resulting hydroxy acid,  
 followed by Curtius rearrangement to introduce the urethane  
 functionality. The scope and versatility of this isostere has been  
 demonstrated by its conversion to potent HIV-1 protease inhibitors  
 with nanomolar potencies. Also, the 3S hydroxyl configuration of  
 the dipeptide isostere I is the preferred configuration for its  
 potency, as established through the synthesis of I (R = Boc) and its  
 3R diastereomer. The present synthesis is efficient and provides an  
 access to other dipeptide mimics with a great deal of structural  
 diversity.

IT 144141-82-2P 144239-47-4P 146500-10-9P

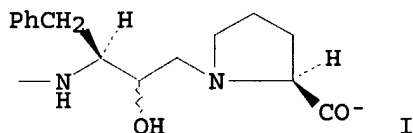
Searcher : Shears 308-4994

146500-11-0P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. and HIV-1 protease inhibitory  
activity of)

L9 ANSWER 68 OF 82 CAPLUS COPYRIGHT 1999 ACS  
AN 1992:644974 CAPLUS  
DN 117:244974  
TI Peptide inhibitors of HIV-1 protease containing phenylnorstatine as  
a transition state element  
AU Raju, Bore G.  
CS Univ. Hosp., Boston, MA, 02118, USA  
SO Pept.: Chem. Biol., Proc. Am. Pept. Symp., 12th (1992), Meeting  
Date 1991, 729-31. Editor(s): Smith, John A.; Rivier, Jean E.  
Publisher: ESCOM, Leiden, Neth.  
CODEN: 57XGA9  
DT Conference  
LA English  
AB To date there are no reports of inhibitors of HIV-1 protease contg.  
phenylnorstatine as the nonhydrolyzable isostere. The present work  
describes the stereochem. requirements for phenylnorstatine to serve  
as a transition state element when incorporated in substrate  
analogs, and explores different substrate sequences as a starting  
point to develop inhibitors of HIV-1 protease. Synthesis of 4  
possible isomers of 3-amino-2-hydroxy-4-phenylbutanoic acid  
(phenylnorstatine, AHPBA) was achieved by a modification of the  
reported procedure. The optically pure amino acids were  
incorporated in peptide sequences by soln. phase techniques. HPLC  
based on HIV-1 protease assay was performed as described.  
IT 137682-13-4 137766-52-0 137766-54-2  
RL: BIOL (Biological study)  
(as HIV-1 protease inhibitor,  
structure in relation to)

L9 ANSWER 69 OF 82 CAPLUS COPYRIGHT 1999 ACS  
AN 1992:592318 CAPLUS  
DN 117:192318  
TI New hydroxyethylamine HIV protease inhibitors that suppress viral  
replication  
AU Rich, Daniel H.; Prasad, J. V. N. Vara; Sun, Chong Qing; Green,  
Jeremy; Mueller, Richard; Houseman, Kathryn; MacKenzie, Debra;  
Malkovsky, Miroslav  
CS Sch. Pharm., Univ. Wisconsin, Madison, WI, 53706, USA  
SO J. Med. Chem. (1992), 35(21), 3803-12  
CODEN: JMCMAR; ISSN: 0022-2623  
DT Journal  
LA English  
OS CJACS  
GI



AB The synthesis of analogs of Ac-Ser-Leu-Asn-[Phe-HEA-Pro]-Ile-Val-OMe (JG-365; Phe-HEA-Pro = hydroxyethylamine transition state analog I), a tight-binding inhibitor of human immunodeficiency virus protease (HIVP), are reported. Systematic modification of the P3 and P3' regions of the inhibitors has led to smaller HIVP inhibitors that inhibit viral replication in HIV-infected and simian immunodeficiency virus (SIV)-infected cell cultures. Six aliph. and arom. derivs. were prepd. by replacing residues in the P3 regions of Boc-Leu-Asn-[Phe-HEA-Pro]-Ile-Val-OMe (Boc = Me<sub>3</sub>CO<sub>2</sub>C). Arom. side chains at P3 gave better inhibitors than aliph. side chains. The better inhibitors in this series contained a .beta.-naphthylalanine or a biphenyl unit at P3. A second series of HIVP inhibitors were obtained by converting the P3 group into acyl groups. R-Asn-[Phe-HEA-Pro]-Ile-Phe-OMe (R = PhCH<sub>2</sub>O<sub>2</sub>C, 2-quinolinylcarbonyl) are potent HIVP inhibitors with K<sub>i</sub> values equal to 1.0 and 0.1 nM, resp. The inhibition consts. were det. by using the continuous fluorometric assay developed by M. V. Toth and G. R. Marshall (1990). The activities of the protease inhibitors for inhibition of SIV replication were detd. in vitro using CEMx174 cells. Inhibition of HIV infection was detd. essentially as reported by R. Pauwels, et. al. (1988). The anti-HIV assay was carried out in culture using CEM cells (a CD4+ lymphocyte line) infected with virus strain HTLV-IIIb with a multiplicity of infection of 0.1. Several analogs inhibited the cytopathic effect at concns. of 0.1-0.8 .mu.g/mL. These results establish that good inhibitors of HIV protease that inhibit viral replication in infected lymphocytes in in vitro cell assays can be obtained from JG-365 when the Ac-Ser-Leu unit is replaced by arom. acyl derivs.

IT 127231-46-3P 127306-17-6P 132234-39-0P  
 132339-14-1P 137515-64-1P 137622-86-7P  
 143347-94-8P 143347-95-9P 143347-96-0P  
 143347-97-1P 143347-98-2P 143347-99-3P  
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 143395-72-6P 143395-73-7P 143395-74-8P  
 143395-75-9P 143395-76-0P 143395-77-1P  
 143395-78-2P 143395-79-3P 143395-80-6P

Searcher : Shears 308-4994



143395-81-7P 143395-82-8P 143395-83-9P

143395-84-0P 143395-85-1P 143395-86-2P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. and HIV protease inhibitory  
activity of)

L9 ANSWER 70 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1992:512027 CAPLUS

DN 117:112027

TI A series of potent HIV-1 protease inhibitors containing a  
hydroxyethyl secondary amine transition state isostere: synthesis,  
enzyme inhibition, and antiviral activity

AU Tucker, Thomas J.; Lumma, William C., Jr.; Payne, Linda S.; Wai,  
Jenny M.; De Solms, S. Jane; Giuliani, Elizabeth A.; Darke, Paul L.;  
Heimbach, Jill C.; Zugay, Joan A.; et al.

CS Merck Res. Lab., West Point, PA, 19486, USA

SO J. Med. Chem. (1992), 35(14), 2525-33

CODEN: JMCMAR; ISSN: 0022-2623

DT Journal

LA English

OS CASREACT 117:112027; CJACS

GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB A series of HIV-1 protease inhibitors contg. a novel hydroxyethyl  
secondary amine transition state isostere, e.g. I [R = Me<sub>3</sub>CO<sub>2</sub>C  
(Boc)] (II), were prep'd. Thus, the alumina-catalyzed ring opening  
of epoxide III with amide IV gave II. The compds. exhibit a strong  
preference for the (R) stereochem. at the transition state hydroxyl  
group. Mol. modeling studies with the prototype compd. II have  
provided important insights into the structural  
requirements for good inhibitor-active site binding interaction.  
N-terminal extension from II into the P2'-P3 region led to the  
discovery of I [R = Qua-Asn (Qua = 2-quinolylcarbonyl)] (V), the  
most potent enzyme inhibitor in the series (IC<sub>50</sub> = 5.4 nM). V was  
shown to have potent antiviral activity in cultured MT-4 human  
T-lymphoid cells. Comparison of analogs of V with analogs of HIV  
protease inhibitor Ro31-8959 demonstrate that considerably different  
structure-activity relationships exist between these two subclasses  
of hydroxyethylamine HIV-protease inhibitors.

IT 142580-65-2P 142580-66-3P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. and human immunodeficiency  
virus-1 protease-inhibiting activity  
of)

Searcher : Shears 308-4994

L9 ANSWER 71 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1992:420008 CAPLUS  
 DN 117:20008  
 TI HIV proteinase inhibitors  
 AU Roberts, Noel A.; Craig, J. Charles; Duncan, Ian B.  
 CS Dep. Chemother., Roche Prod. Ltd., Welwyn Garden City/Herts, AL7 3AY, UK  
 SO Biochem. Soc. Trans. (1992), 20(2), 513-16  
 CODEN: BCSTB5; ISSN: 0300-5127  
 DT Journal  
 LA English  
 AB The development and mode of action of the HIV proteinase inhibitor Ro 318959 is discussed. Antiviral efficacy and an additive inhibition of HIV-1 with dideoxycytidine and AZT are shown.  
 IT 127779-20-8  
 RL: BIOL (Biological study)  
 (human immunodeficiency virus  
 inhibition by, aspartic proteinase inhibition  
 in)

L9 ANSWER 72 OF 82 CAPLUS COPYRIGHT 1999 ACS  
 AN 1992:227702 CAPLUS  
 DN 116:227702  
 TI Intriguing structure-activity relations underlie the potent inhibition of HIV protease by norstatine-based peptides  
 AU Tam, Tim F.; Carriere, Julie; MacDonald, I. David; Castelhana, Arlindo L.; Pliura, Diana H.; Dewdney, Nolan J.; Thomas, Everton M.; Bach, Chinh; Barnett, Jimmy; et al.  
 CS Syntex Res. Canada, Mississauga, ON, L5N 3X4, Can.  
 SO J. Med. Chem. (1992), 35(7), 1318-20  
 CODEN: JMCMAR; ISSN: 0022-2623  
 DT Journal  
 LA English  
 OS CJACS  
 AB Phenylnorstatine contg. peptides extending from the P2 to P1' positions, with L-proline at the P1' position and S-stereochem. of the P1 component, exhibit impressive potency vs. HIV-1 protease (IC50 = 0.58-7.4 nM). Representative ketoamides are also active with slightly lower potency. Analogous hydroxyethylamines have previously been reported to be potent inhibitors of this enzyme. The presence of an addnl. carbonyl in this series of proline-based inhibitors enhances their potency, and alters structure-activity relations profoundly. Whereas divergent effects on potency have been obsd. for epimeric hydroxyethylamines upon extension of such P1' terminal peptides to P3' with Ile-Val, lengthening of norstatine contg.-inhibitors in the same fashion, dramatically increases the potency of the R-diastereomer and leaves the IC50 of the S-epimer essentially unchanged. Most interestingly, amino acid residues in  
 Searcher : Shears 308-4994

the P1' position contg. parent and fused piperidines lower activity in the norstatine series. By contrast, significant enhancements in inhibitor potency were reported in the hydroxyethylamine series for such proline replacements. Conformational preferences of 6 member rings influenced by A1,3-strain may contribute to the redn. in potency obsd. for the norstatine contg. peptides.

IT 132234-32-3 132339-14-1 137515-64-1  
137622-86-7 139694-65-8 139758-12-6  
141171-72-4 141171-73-5 141171-74-6  
141171-76-8 141171-77-9 141171-78-0  
141171-79-1 141171-80-4 141171-81-5  
141171-82-6 141197-75-3 141269-68-3

RL: BIOL (Biological study)

(human immunodeficiency virus 1  
protease inhibition by)

L9 ANSWER 73 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1992:143332 CAPLUS

DN 116:143332

TI KNI-102, a novel tripeptide HIV protease inhibitor containing allophenylnorstatine as a transition-state mimic

AU Mimoto, Tsutomu; Imai, Junya; Tanaka, Shigeki; Hattori, Naoko; Kisanuki, Sumitsugu; Akaji, Kenichi; Kiso, Yoshiaki

CS Dep. Med. Chem., Kyoto Pharm. Univ., Kyoto, 607, Japan

SO Chem. Pharm. Bull. (1991), 39(11), 3088-90

CODEN: CPBTAL; ISSN: 0009-2363

DT Journal

LA English

AB HIV-1 protease inhibitors contg. allophenylnorstatine [Apns; (2S,3S)-3-amino-2-hydroxy-4-phenylbutyric acid]-Pro (syn diastereomer) as a transition-state mimic were established to be potent and highly selective. Z-Asn-Apns-Pro-NHBut (KNI-102) is the only tripeptide exhibiting substantial anti-HIV activity and may be of min. size for potent, selective inhibition of HIV protease. Ready availability due to its simple chem. structure and stability should make it valuable for studies of the development of metabolically stable anti-AIDS drugs.

IT 138228-18-9, KNI 122 138228-19-0  
138228-20-3 138228-21-4 138258-64-7, KNI  
93 139694-65-8, KNI 102 139694-67-0  
139757-45-2 139758-09-1, KNI 81  
139758-10-4 139758-11-5 139758-12-6

RL: BIOL (Biological study)

(as HIV protease inhibitor,  
structure in, antiviral activity in relation to)

L9 ANSWER 74 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1992:120368 CAPLUS

DN 116:120368

Searcher : Shears 308-4994

TI Novel binding mode of highly potent HIV-proteinase inhibitors  
incorporating the (R)-hydroxyethylamine isostere

AU Krohn, Antonin; Redshaw, Sally; Ritchie, Jenny C.; Graves, Bradford  
J.; Hatada, Marcos H.

CS Roche Prod. Ltd., Welwyn Garden City/Hertfordshire, AL7 3AY, UK

SO J. Med. Chem. (1991), 34(11), 3340-2  
CODEN: JMCMAR; ISSN: 0022-2623

DT Journal

LA English

OS CJACS

AB A series of new HIV-1 proteinase (HIV-PR) inhibitors incorporating  
hydroxyethylamine transition state mimetic has been designed and  
synthesized. The stereochem. requirement at the hydroxyl group has  
been found to depend critically both upon the length of the  
inhibitor and upon the nature of individual residues. Small, highly  
potent inhibitors contg. the (S,S,S)-decahydroisoquinoline-3-carboxy  
group in the P1' position show a marked preference for the R  
configuration at the alc. The x-ray structure of the  
HIV-PR-Ro31-8959 complex revealed a novel binding mode of the  
inhibitor to the enzyme.

IT 127231-42-9 127231-45-2 132748-20-0  
RL: BIOL (Biological study)  
(HIV-protease inhibitor,  
hydroxyethylamine isostere in, binding mode of)

IT 137515-64-1P 137515-65-2P 137622-86-7P  
137622-87-8P  
RL: BAC (Biological activity or effector, except adverse); SPN  
(Synthetic preparation); THU (Therapeutic use); BIOL (Biological  
study); PREP (Preparation); USES (Uses)  
(prepn. of, as HIV protease inhibitor  
, hydroxyethylamine isostere in, binding mode of)

IT 127779-20-8P 136522-18-4P 137622-85-6P  
137693-11-9P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, as HIV-protease inhibitor  
, hydroxyethylamine isostere in, binding mode in)

L9 ANSWER 75 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1991:670042 CAPLUS

DN 115:270042

TI Inhibitor stabilization of human immunodeficiency virus type-2  
proteinase dimer formation

AU Holzman, Thomas F.; Kohlbrenner, William E.; Weigl, Debra;  
Rittenhouse, Judith; Kempf, Dale; Erickson, John

CS Pharm. Prod. Div., Abbott Lab., Abbott Park, IL, 60064, USA

SO J. Biol. Chem. (1991), 266(29), 19217-20  
CODEN: JBCHA3; ISSN: 0021-9258

DT Journal

LA English

AB The authors report the first direct observation of the subunit self-assocn. behavior of highly purified recombinant human immunodeficiency virus type-2 (HIV-2) proteinase. Multiple samples of enzyme were subjected to sedimentation equil. anal. ultracentrifugation sequentially at 8.8.degree. and two pH values in the presence and absence of the C2 sym., peptidomimetic inhibitor A76889. At both pH values the enzyme exhibited sedimentation equil. behavior which fit a monomer-dimer-tetramer model. In the absence of inhibitor, the apparent Kd for dimer formation was less than .apprx.100 .mu.M and the apparent Kd for the weaker dimer-tetramer assocn. was greater than .apprx.100 .mu.M. In the presence of inhibitor, at either pH, dimer formation was more strongly favored as indicated by a .apprx.5-14-fold decrease in the apparent Kd for dimer formation and a .apprx.1.2-4-fold increase in the apparent Kd for tetramer formation. The enhanced formation of dimer and decrease in higher order self-assocd. forms in the presence of an inhibitor is consistent with inhibitor stabilization of an active dimer. The inhibitor-induced stabilization of the dimeric species is consistent with a model for substrate-induced formation of active proteinase dimers in virion assembly.

IT 137545-03-0, A 76889

RL: BIOL (Biological study)  
(human immunodeficiency virus type  
2 proteinase inhibitor, proteinase dimer  
formation stabilization by)

L9 ANSWER 76 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1991:656656 CAPLUS

DN 115:256656

TI Preparation of proline- and asparagine-containing peptides as HIV protease inhibitors

IN Marshall, Garland R.; Rich, Daniel H.; Green, Jeremy; Sun, Chongqing

PA Wisconsin Alumni Research Foundation, USA

SO PCT Int. Appl., 31 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9108221	A1	19910613	WO 90-US7059	19901203

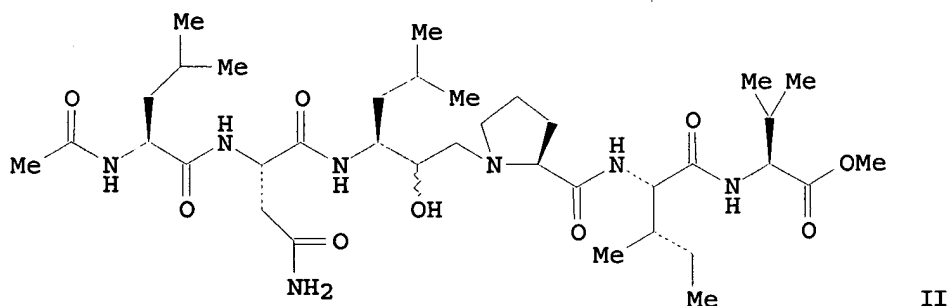
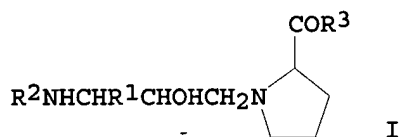
W: JP, US

RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE

PRAI US 89-445070 19891204

OS MARPAT 115:256656

GI



AB Proline- and asparagine-contg. peptides I ( $R_1 = \text{Me}_2\text{CHCH}_2, \text{CH}_2\text{Ph}, \text{cyclohexylmethyl}, \text{alkyl or aralkyl group contg. } <12 \text{ C atoms}; R_2, R_3 = \text{peptidyl residue where } R_2 \text{ and } R_3 \text{ each contain at least one amino acid residue and at least one of } R_2 \text{ or } R_3 \text{ has at least 2 amino acid residues}; R_2 \text{ contains Asn residue and } R_2 \text{ may contain } R_4\text{CO}, \text{ where } R_4 = \text{aryl}) \text{ which are protected at both ends by, e.g., 2-aminobenzoic acid at one end, were prepd. as HIV protease inhibitors. Thus, 3S-amino-1-chloro-5-methyl-2-hexanone hydrochloride (prepn. from Boc-Leu-OH.cntdot.H<sub>2</sub>O given) was coupled with Boc-Asn-OH and the resulting dipeptide was coupled with Boc-Leu-OH and deprotected to give Ac-Leu-Asn-Leu-CH<sub>2</sub>Cl. This was condensed with Pro-Ile-Val-OMe.cntdot.TosOH (prepn. given) in DMF contg. NaI and NaHCO<sub>3</sub> and the resulting aminoketone was reduced by NaBH<sub>4</sub> to give title compd. II. I have IC<sub>50</sub>'s < 1 nM against HIV protease.$

IT 137150-30-2P 137150-31-3P 137150-32-4P  
137150-33-5P 137150-34-6P 137253-05-5P  
137253-06-6P 137328-41-7P 137328-43-9P  
137328-44-0P 137328-45-1P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation) (prepn. of, as HIV protease inhibitor)

L9 ANSWER 77 OF 82 CAPLUS COPYRIGHT 1999 ACS  
AN 1991:656637 CAPLUS  
DN 115:256637

TI Preparation of N-(asparaginylaminohydroxyphenylbutyl)decahydroisoquinidine-3-carboxamides as HIV protease inhibitors

IN Martin, Joseph Armstrong; Redshaw, Sally

PA Hoffmann-La Roche, F., A.-G., Switz.

Searcher : Shears 308-4994

SO Eur. Pat. Appl., 17 pp.

CODEN: EPXXDW

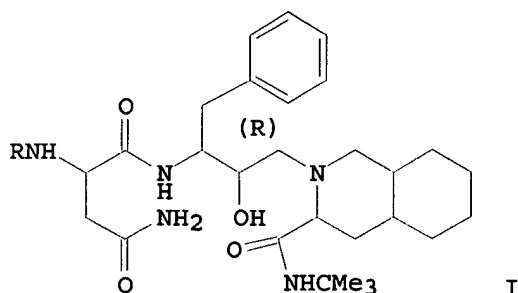
DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 432695	A2	19910619	EP 90-123697	19901210
	EP 432695	A3	19911218		
	EP 432695	B1	19950517		
	R: AT, BE, CH, DE, DK, ES, FR, GR, IT, LI, LU, NL, SE				
	IN 172553	A	19930925	IN 90-MA905	19901112
	US 5196438	A	19930323	US 90-615534	19901119
	CA 2030433	AA	19910612	CA 90-2030433	19901121
	CA 2030433	C	19971021		
	CZ 280558	B6	19960214	CZ 90-5765	19901121
	FI 9005983	A	19910612	FI 90-5983	19901204
	ZA 9009743	A	19910828	ZA 90-9743	19901204
	RO 107942	B1	19940131	RO 90-146474	19901204
	HU 56073	A2	19910729	HU 90-8076	19901205
	HU 207298	B	19930329		
	IL 96550	A1	19950315	IL 90-96550	19901205
	AU 9067876	A1	19910613	AU 90-67876	19901207
	AU 634319	B2	19930218		
	NO 9005322	A	19910612	NO 90-5322	19901210
	NO 176566	B	19950116		
	NO 176566	C	19950426		
	GB 2239016	A1	19910619	GB 90-26776	19901210
	GB 2239016	B2	19930804		
	CN 1052482	A	19910626	CN 90-109931	19901210
	CN 1034805	B	19970507		
	BR 9006264	A	19910924	BR 90-6264	19901210
	JP 03255076	A2	19911113	JP 90-409792	19901210
	ES 2072959	T3	19950801	ES 90-123697	19901210
	CN 1138983	A	19970101	CN 96-107466	19901210
	PL 165225	B1	19941130	PL 90-288201	19901211
	RU 2071470	C1	19970110	RU 90-4831985	19901211
	LT 3682	B	19960125	LT 93-862	19930816
	FI 9703895	A	19971006	FI 97-3895	19971006
PRAI	GB 89-27913		19891211		
	FI 90-5983		19901204		

GI



AB Title compds. (I; R = PhCH<sub>2</sub>O<sub>2</sub>C, 2-quinolinecarbonyl; all undesigned chiral centers are S) were prepd. Thus, N-tert-butyldecahydro-(4aS,9aS)-isoquinoline-(3S)-carboxamide (prepn. given) was condensed with (3S)-benzyloxyformamido-1,2(S)-epoxy-4-phenylbutane in EtOH at 20.degree. over 16 h; the product was hydrogenated and the free amine was coupled with Z-Asn-OH in THF using hydroxybenzotriazole, N-ethylmorpholine, and DCC with ice/salt cooling to give I (R = PhCH<sub>2</sub>O<sub>2</sub>C). The latter inhibited HTLV-III infection of C8166 cells with I<sub>50</sub> = 20 nM.

IT 127779-20-8P 136522-18-4P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation) (prepn. of, as HIV protease inhibitor)

L9 ANSWER 78 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1990:612686 CAPLUS

DN 113:212686

TI Peptide analogs as human immunodeficiency virus (HIV) protease inhibitors

IN Hanko, Rudolf H.; Scangos, George A.; Yoo-Warren, Heeja; Ramabhadran, Triprayar V.; Paessens, Arnold; Henning, Rolf; Tamburini, Paul Perry; Hoppe, Dieter; Hansen, Jutta; Rabe, Klaus

PA Molecular Therapeutics, Inc., USA

SO Eur. Pat. Appl., 73 pp.

CODEN: EPXXDW

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 361341	A2	19900404	EP 89-117616	19890923
	EP 361341	A3	19910703		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	FI 8904541	A	19900329	FI 89-4541	19890926
	AU 8942308	A1	19900816	AU 89-42308	19890926

Searcher : Shears 308-4994



AU 633017 B2 19930121  
DK 8904760 A 19900329 DK 89-4760 19890927  
NO 8903834 A 19900329 NO 89-3834 19890927  
ZA 8907338 A 19900725 ZA 89-7338 19890927  
JP 02191243 A2 19900727 JP 89-253683 19890928  
PRAI US 88-250472 19880928  
US 89-386194 19890801  
OS MARPAT 113:212686  
GI For diagram(s), see printed CA Issue.  
AB AlkZnYmA2 [A1 = H, R1CO; R1 = OR2, NR2R3, CR2R3R4; R2, R3, R4 =  
(substituted) alipharyl, aryl; k, n = 0, 1, k = 0 when Z = H; n = 0  
when Y = H; Z = H, Ser, Thr, R1CO; Y = H, R5CO; R5 = R1, HNCHR9CO;  
R9 = (substituted) alipharyl; A2 = E4E2QE1X, etc; E4 = H, Asn, R1CO;  
E2 = HNCH(CH2R6)CH(OH)CH2, HNCH(CH2R6)P(OH)(O), etc.; Q =  
4-7-membered (hetero)cyclylene; E1 = CO; X = H, R1, HNCHR7R10; R6,  
R7 = (substituted) alipharyl, aryl; R10 = H, COR1, CONHCHR9COR1],  
were prepd. Thus, title compd. I, prepd. by soln. phase methods,  
had an IC50 of 8 .mu.M for inhibition of HIV protease.  
IT 130371-70-9P 130371-71-0P 130371-72-1P  
130371-73-2P 130371-74-3P 130371-75-4P  
130371-76-5P 130371-77-6P 130371-78-7P  
130371-79-8P 130371-81-2P  
RL: BAC (Biological activity or effector, except adverse); SPN  
(Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(prepn. of, as HIV protease inhibitor  
)  
L9 ANSWER 79 OF 82 CAPLUS COPYRIGHT 1999 ACS  
AN 1990:544869 CAPLUS  
DN 113:144869  
TI Structure-based, C2 symmetric inhibitors of HIV protease  
AU Kempf, Dale J.; Norbeck, Daniel W.; Codacovi, LynnMarie; Wang, Xiu  
Chun; Kohlbrenner, William E.; Wideburg, Norman E.; Paul, Deborah  
A.; Knigge, Mark F.; Vasavanonda, Sudthida; et al.  
CS Pharm. Prod. Div., Abbott Lab., Abbott Park, IL, 60064, USA  
SO J. Med. Chem. (1990), 33(10), 2687-9  
CODEN: JMCMAR; ISSN: 0022-2623  
DT Journal  
LA English  
OS CJACS  
AB Novel inhibitors of human immunodeficiency virus 1 (HIV-1) protease,  
an essential enzyme for the replication of HIV, are described.  
Based on the unique C2 sym., homodimeric structure of HIV protease,  
sym. and pseudosym. inhibitors were designed and synthesized. These  
compds. specifically inhibit HIV protease at subnanomolar concns.  
and block acute HIV infections in vitro at 20-150 nM.  
IT 129467-48-7P 129467-49-8P 129467-50-1P  
129491-63-0P 129491-64-1P 129491-65-2P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
Searcher : Shears 308-4994

(prepn. and HIV-1 protease inhibition  
by)

L9 ANSWER 80 OF 82 CAPLUS COPYRIGHT 1999 ACS  
AN 1990:441332 CAPLUS  
DN 113:41332  
TI Preparation of peptide amides as human immunodeficiency virus  
inhibitors  
IN Handa, Balraj Krishan; Machin, Peter James; Martin, Joseph  
Armstrong; Redshaw, Sally; Thomas, Gareth John  
PA Hoffmann-La Roche, F., und Co. A.-G., Switz.  
SO Eur. Pat. Appl., 69 pp.  
CODEN: EPXXDW  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 346847	A2	19891220	EP 89-110717	19890613
	EP 346847	A3	19911023		
	EP 346847	B1	19940511		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	US 5157041	A	19921020	US 89-362621	19890605
	ZA 8904285	A	19900228	ZA 89-4285	19890606
	AU 8936130	A1	19891214	AU 89-36130	19890607
	AU 624144	B2	19920604		
	HU 51254	A2	19900428	HU 89-2903	19890607
	HU 205898	B	19920728		
	DK 8902863	A	19891214	DK 89-2863	19890612
	NO 8902407	A	19891214	NO 89-2407	19890612
	NO 175715	B	19940815		
	NO 175715	C	19941123		
	JP 02042048	A2	19900213	JP 89-149265	19890612
	JP 2515019	B2	19960710		
	FI 8902881	A	19891214	FI 89-2881	19890613
	FI 95693	B	19951130		
	FI 95693	C	19960311		
	AT 105549	E	19940515	AT 89-110717	19890613
	ES 2052815	T3	19940716	ES 89-110717	19890613
	US 5446161	A	19950829	US 92-916812	19920720
	US 5554756	A	19960910	US 95-391380	19950217
	US 5652369	A	19970729	US 95-394523	19950406
	US 5620987	A	19970415	US 95-398478	19950410
PRAI	GB 88-13940		19880613		
	GB 89-8035		19890410		
	US 89-362621		19890605		
	EP 89-110717		19890613		
	US 92-916812		19920720		
OS	MARPAT 113:41332				

Searcher : Shears 308-4994

AB R1R2NCHR3CONHCHR4CR5R6CH2N(:O)nR7CHR8R9 [I; R1 = alkoxycarbonyl, aralkoxycarbonyl, (ar)alkanoyl, cycloalkylcarbonyl, aroyl, heterocyclylcarbonyl, alkylsulfonyl, etc.; R2 = H; R1R2N = cyclic arom. imide; R3 = (cyclo)alkyl, (aryl)alkyl, aryl, heterocyclylalkyl, cyanoalkyl, etc; R4 = alkyl, cycloalkyl(alkyl), aryl(alkyl); R5 = H; R6 = OH; R5R6 = :O; R7R8 = (un)substituted (CH2)3, (CH2)4, with 1 CH2 optionally replaced by NH, N(acyl), S, etc., optionally carrying 1 fused cycloalkane or (hetero)arom. ring; R9 = alkoxycarbonyl, monoalkylcarbamoyl, CONHCHR10CONHR11; R10, R11 = alkyl; n = 0, 1] and their pharmaceutically acceptable salts were prep'd., e.g., by coupling amines H2NCHR4CR5R6CH2NR7CHR8R9 with acids R1R2NCHR3CO2H. Thus, N1-isobutyl-L-isoleucylamide (prepn. given) was coupled with Z-proline succinimide ester (Z = benzyloxycarbonyl), the resulting dipeptide was deprotected and coupled with (Z-phenylalanyl)methyl bromide, the intermediate tripeptide reduced by NaBH4 in EtOH, deprotected, and coupled with Z-Asn-OH to give N2-[N-[3(S)-[(Z-asparaginyl)amino]-2(R,S)-hydroxy-4-phenylbutyl]-L-prolyl]-N1-isobutyl-L-isoleucylamide. One (unspecified) of 2 isomers of the latter in vitro inhibited human immunodeficiency virus protease with an IC50 of 0.13 .mu.M. IC50 values reported for 7 other I ranged from 0.01-0.87 .mu.M.

IT 127749-93-3P 127749-94-4P 128018-12-2P  
 128018-26-8P 128018-42-8P 128018-49-5P  
 128018-67-7P 128018-74-6P 128018-75-7P  
 128018-76-8P 128018-77-9P 128018-78-0P  
 128018-89-3P 128018-91-7P 128018-92-8P  
 128018-93-9P 128018-94-0P 128018-95-1P  
 128018-96-2P 128018-97-3P 128018-98-4P  
 128018-99-5P 128019-05-6P 128019-06-7P  
 128019-08-9P 128019-13-6P 128019-14-7P  
 128019-23-8P 128019-24-9P 128019-39-6P  
 128019-47-6P 128019-48-7P 128019-49-8P  
 128019-50-1P 128019-53-4P 128019-54-5P  
 128019-55-6P 128019-56-7P 128019-70-5P  
 128019-76-1P 128019-82-9P 128019-94-3P  
 128043-05-0P 128043-06-1P 128053-23-6P  
 128053-24-7P 128053-27-0P 128053-31-6P  
 128053-33-8P 128053-40-7P 128053-42-9P  
 128053-46-3P 128111-39-7P 128111-40-0P  
 128111-44-4P

RL: BAC (Biological activity or effector, except adverse); SPN  
 (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
 (prepn. of, as HIV protease inhibitor  
 )

L9 ANSWER 81 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1990:417492 CAPLUS

DN 113:17492

TI Rational design of peptide-based HIV proteinase inhibitors

Searcher : Shears 308-4994

AU Roberts, Noel A.; Martin, Joseph A.; Kinchington, Derek; Broadhurst, Anne V.; Craig, J. Charles; Duncan, Ian B.; Galpin, Sarah A.; Handa, Balraj K.; Kay, John; et al.

CS Roche Prod. Ltd., Welwyn Garden City/Hertfordshire, AL7 3AY, UK

SO Science (Washington, D. C., 1883-) (1990), 248(4953), 358-61  
CODEN: SCIEAS; ISSN: 0036-8075

DT Journal

LA English

AB A series of peptide derivs. based on the transition-state mimetic concept has been designed that inhibit the proteinase from the human immunodeficiency virus (HIV). The more active compds. inhibit both HIV-1 and HIV-2 proteinases in the nanomolar range with little effect at 10 micromolar against the structurally related human aspartic proteinases. Proteolytic cleavage of the HIV-1 gag polyprotein (p55) to the viral structural protein p24 was inhibited in chronically infected CEM cells. Antiviral activity was obsd. in the nanomolar range (with one compd. active below 10 nanomolar) in three different cell systems, as assessed by p24 antigen and syncytium formation. Cytotoxicity was not detected at 10 and 5 micromolar in C8166 and JM cells, resp., indicating a high therapeutic index for this new class of HIV proteinase inhibitors.

IT 127749-93-3 127749-94-4 127749-95-5  
127779-20-8  
RL: BIOL (Biological study)  
(as human immunodeficiency virus  
proteinase inhibitor, antiviral activity and  
cytotoxicity of, structure in relation to)

L9 ANSWER 82 OF 82 CAPLUS COPYRIGHT 1999 ACS

AN 1990:406798 CAPLUS

DN 113:6798

TI Hydroxyethylamine analogs of the p17/p24 substrate cleavage site are tight-binding inhibitors of HIV protease

AU Rich, Daniel H.; Green, Jeremy; Toth, Mihaly V.; Marshall, Garland R.; Kent, Stephen B. H.

CS Sch. Pharm., Univ., Madison, WI, 53706, USA

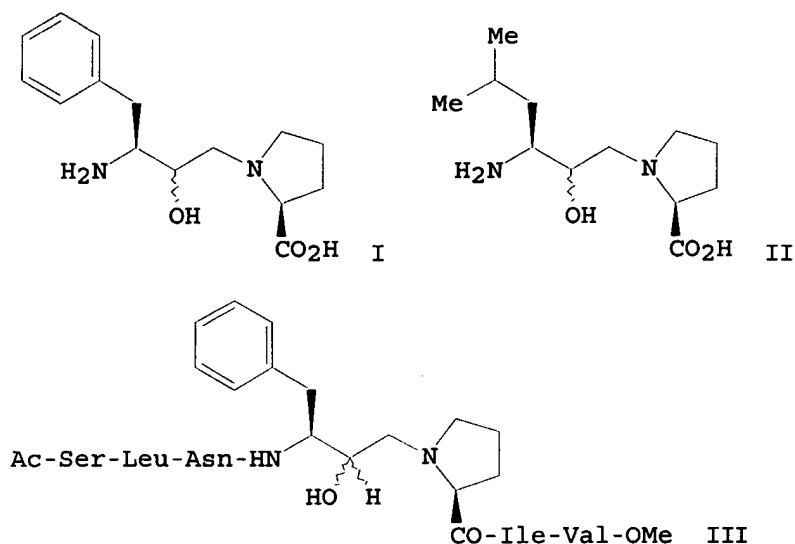
SO J. Med. Chem. (1990), 33(5), 1285-8  
CODEN: JMCMAR; ISSN: 0022-2623

DT Journal

LA English

OS CASREACT 113:6798; CJACS

GI



AB Hydroxyethylamine (HEA) dipeptidyl isosteres I and II were designed to mimic the tetrahedral intermediate for the hydrolysis of Tyr-Pro, one of the partial substrate sequences cleaved by HIV protease. Incorporation of hydroxyethylamines I and II in peptides related to the p17/p24 substrate sequence produces tight-binding inhibitors of HIV protease. HEA inhibitor III has a  $K_i = 0.66$  nM.

IT 127231-45-2P 127231-46-3P 127231-47-4P  
127231-48-5P 127231-49-6P 127231-50-9P  
127231-51-0P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation) (prepn. of, as HIV protease inhibitor)

=> sel hit 19 1-82 rn

E1 THROUGH E944 ASSIGNED

=> fil reg

FILE 'REGISTRY' ENTERED AT 12:32:38 ON 29 JAN 1999  
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STRUCTURE FILE UPDATES: 23 JAN 99 HIGHEST RN 217939-24-7  
DICTIONARY FILE UPDATES: 28 JAN 99 HIGHEST RN 217939-24-7

Searcher : Shears 308-4994

TSCA INFORMATION NOW CURRENT THROUGH JUNE 29, 1998

Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

=> d que l10; d que l11; d que l12; d que l13; d que l14; s l10 or l11 or l12 or l13 or  
l14

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Searcher : Shears 308-4994

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L15 943 L10 OR L11 OR L12 OR L13 OR L14

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Searcher : Shears 308-4994

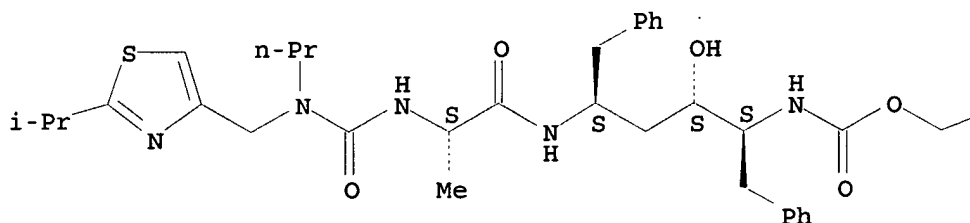
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS

IN 2,7,10,12-Tetraazapentadecanoic acid, 4-hydroxy-9-methyl-12-[[2-(1-methylethyl)-4-thiazolyl]methyl]-8,11-dioxo-3,6-bis(phenylmethyl)-, 5-thiazolylmethyl ester, [3S-(3R\*,4R\*,6R\*,9R\*)] - (9CI)

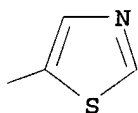
MF C37 H48 N6 O5 S2

Absolute stereochemistry.

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HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):24

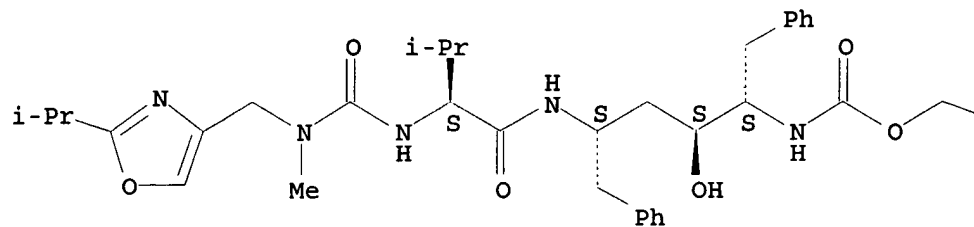
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS

IN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-oxazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 3-pyridinylmethyl ester, [5S-(5R\*,8R\*,10R\*,11R\*)] - (9CI)

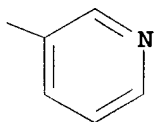
MF C39 H50 N6 O6

Absolute stereochemistry.

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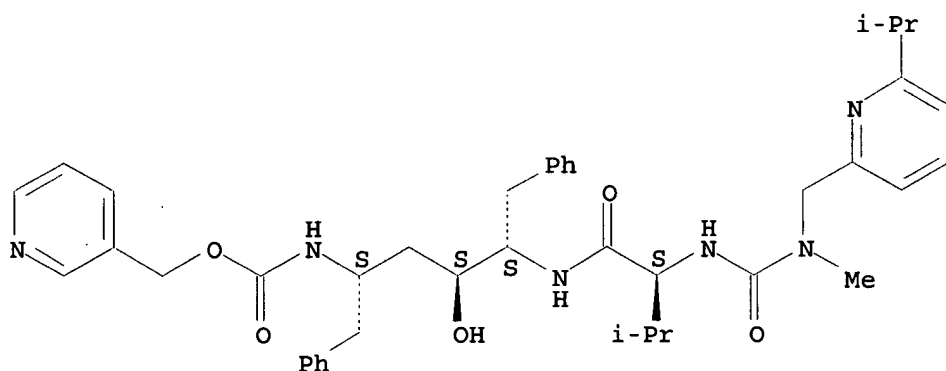


L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS

IN 2,4,7,12-Tetraazatridecan-13-oic acid, 9-hydroxy-2-methyl-5-(1-methylethyl)-1-[6-(1-methylethyl)-2-pyridinyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 3-pyridinylmethyl ester, [5S-(5R\*,8R\*,9R\*,11R\*)]-(9CI)

MF C41 H52 N6 O5

Absolute stereochemistry.



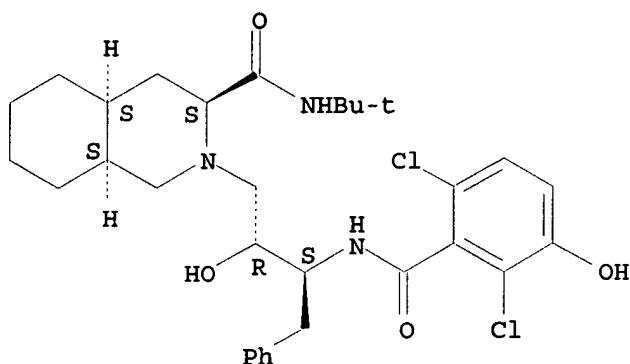
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS

IN 3-Isoquinolinecarboxamide, 2-[3-[(2,6-dichloro-3-  
Searcher : Shears 308-4994

hydroxybenzoyl) amino] -2-hydroxy-4-phenylbutyl] -N- (1,1-dimethylethyl) decahydro-, [3S- [2(2S\*,3R\*), 3.alpha., 4a.beta., 8a.beta.]] - (9CI)

MF C31 H41 Cl2 N3 O4

Absolute stereochemistry.



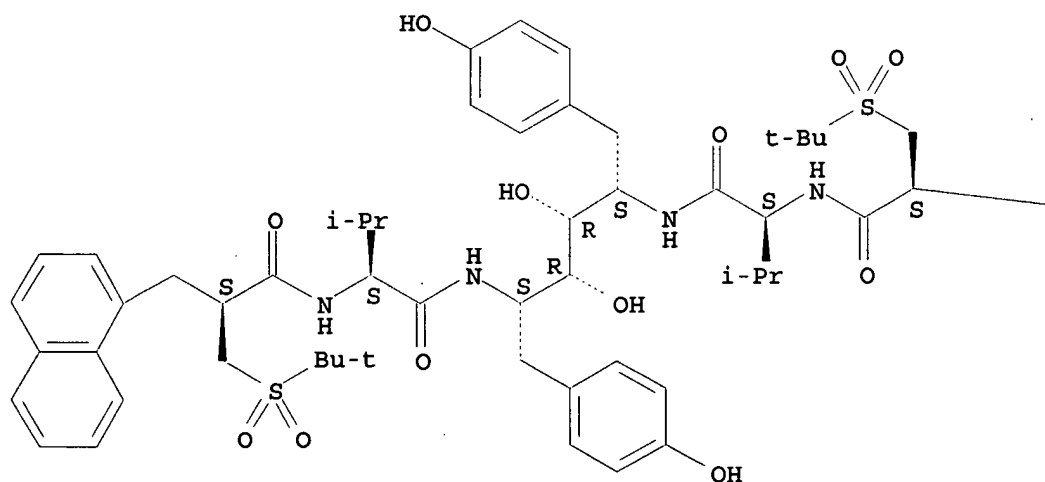
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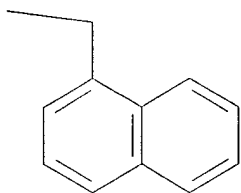
IN L-Iditol, 1,2,5,6-tetra-deoxy-2,5-bis[[2-[[2-[[[(1,1-dimethylethyl)sulfonyl]methyl]-3-(1-naphthalenyl)-1-oxopropyl]amino]-3-methyl-1-oxobutyl]amino]-1,6-bis(4-hydroxyphenyl)-, [2[S(S)],5[S(S)]] - (9CI)

MF C64 H82 N4 O12 S2

Absolute stereochemistry.

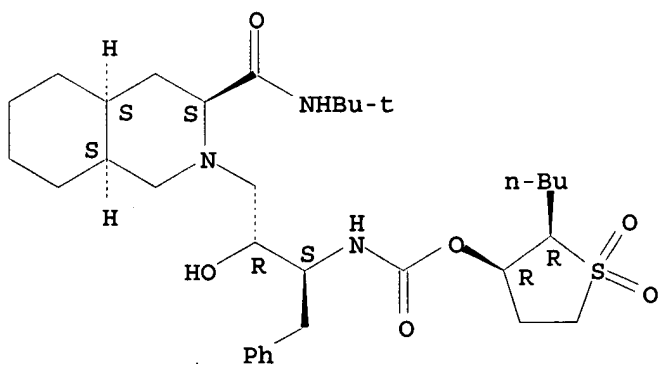
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L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS  
 IN Carbamic acid, [3-[3-[[[(1,1-dimethylethyl)amino]carbonyl]octahydro-  
 2(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]-,  
 2-butyltetrahydro-1,1-dioxido-3-thienyl ester, [3S-  
 [2[1R\*(2S\*,3S\*),2S\*],3.alpha.,4a.beta.,8a.beta.]]- (9CI)  
 MF C33 H53 N3 O6 S

Absolute stereochemistry.

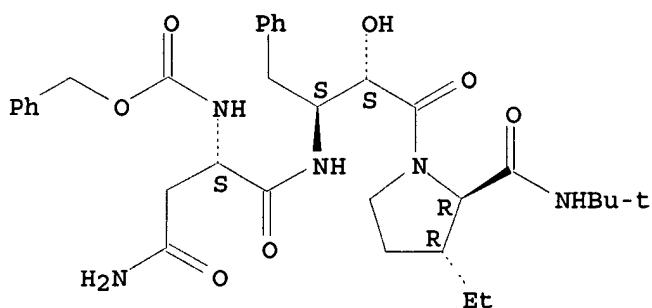


L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS  
 IN Carbamic acid, [3-amino-1-[[[3-[2-[[[(1,1-  
 dimethylethyl)amino]carbonyl]-3-ethyl-1-pyrrolidinyl]-2-hydroxy-3-  
 oxo-1-(phenylmethyl)propyl]amino]carbonyl]-3-oxopropyl]-,  
 phenylmethyl ester, [2R-[1[1S\*(S\*),2S\*],2.alpha.,3.beta.]]- (9CI)  
 MF C33 H45 N5 O7

Searcher : Shears 308-4994



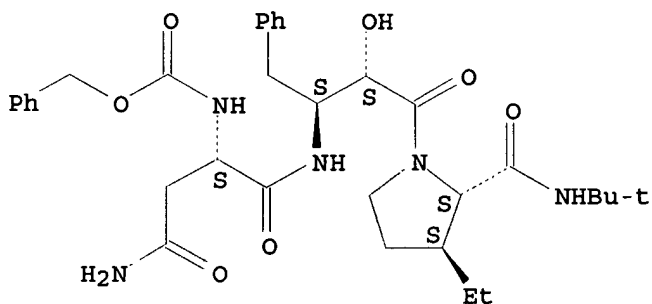
Absolute stereochemistry.



C82-Asn

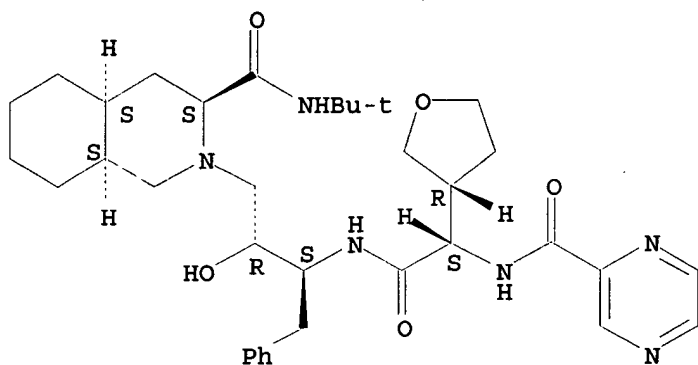
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS  
 IN Carbamic acid, [3-amino-1-[[[3-[2-[[[1,1-dimethylethyl)amino]carbonyl]-3-ethyl-1-pyrrolidinyl]-2-hydroxy-3-oxo-1-(phenylmethyl)propyl]amino]carbonyl]-3-oxopropyl]-, phenylmethyl ester, [2S-[1[1R\*(R\*),2R\*],2.alpha.,3.beta.]]- (9CI)  
 MF C33 H45 N5 O7

Absolute stereochemistry.



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS  
 IN 3-Isoquinolinecarboxamide, N-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-4-phenyl-3-[[[(pyrazinylcarbonyl)amino](tetrahydro-3-furanyl)acetyl]amino]butyl]-, [3S-[2[2S\*,3R\*[R\*(S\*)]],3.alpha.,4a.beta.,8a.beta.]]- (9CI)  
 MF C35 H50 N6 O5

Absolute stereochemistry.



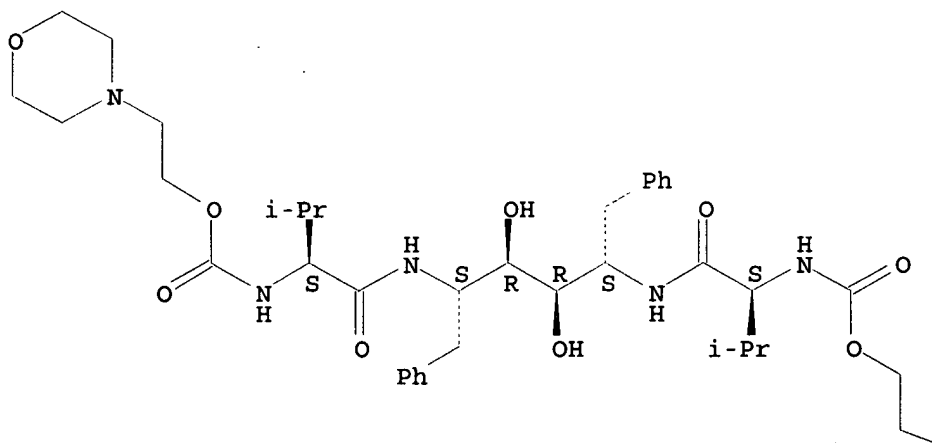
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS

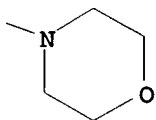
IN L-Iditol, 1,2,5,6-tetradeoxy-2,5-bis[[3-methyl-2-[[[2-(4-morpholinyl)ethoxy]carbonyl]amino]-1-oxobutyl]amino]-1,6-diphenyl-, [2(S),5(S)]- (9CI)

MF C42 H64 N6 O10

Absolute stereochemistry.

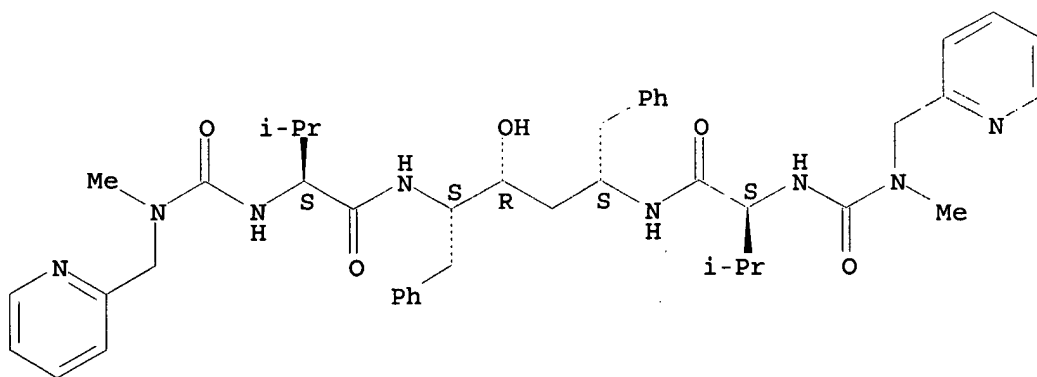
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L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS  
 IN 2,5,10,13-Tetraazatetradecanedi-7-amine, 7-hydroxy-N,N'-dimethyl-3,12-bis(1-methylethyl)-4,11-dioxo-6,9-bis(phenylmethyl)-N,N'-bis(2-pyridinylmethyl)-, [3S-(3R\*,6R\*,7S\*,9R\*,12R\*)]- (9CI)  
 MF C44 H58 N8 O5

Absolute stereochemistry.



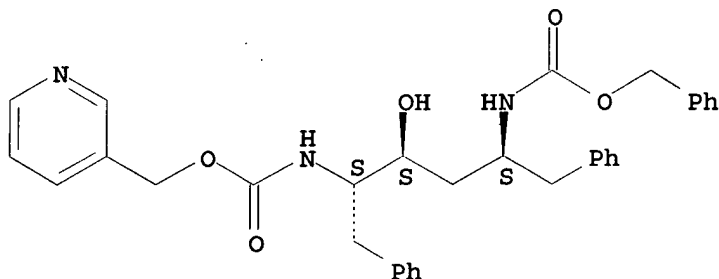
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS  
 IN Carbamic acid, [2-hydroxy-5-phenyl-4-[[[(phenylmethoxy)carbonyl]amino]-1-(phenylmethyl)pentyl]-, 3-pyridinylmethyl ester,  
 Searcher : Shears 308-4994

PCT/25964

[1S-(1R\*,2R\*,4R\*)]- (9CI)

MF C33 H35 N3 O5

Absolute stereochemistry.

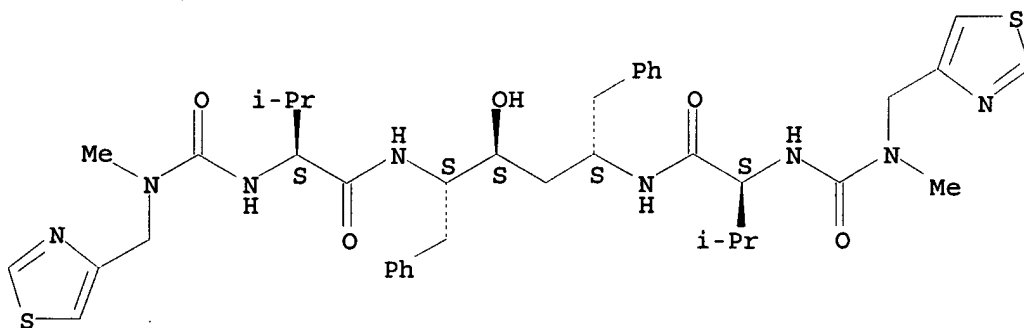


L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS

IN 2,5,10,13-Tetraazatetradecanediamide, 7-hydroxy-N,N'-dimethyl-3,12-bis(1-methylethyl)-4,11-dioxo-6,9-bis(phenylmethyl)-N,N'-bis(4-thiazolylmethyl)-, [3S-(3R\*,6R\*,7R\*,9R\*,12R\*)]- (9CI)

MF C40 H54 N8 O5 S2

Absolute stereochemistry.



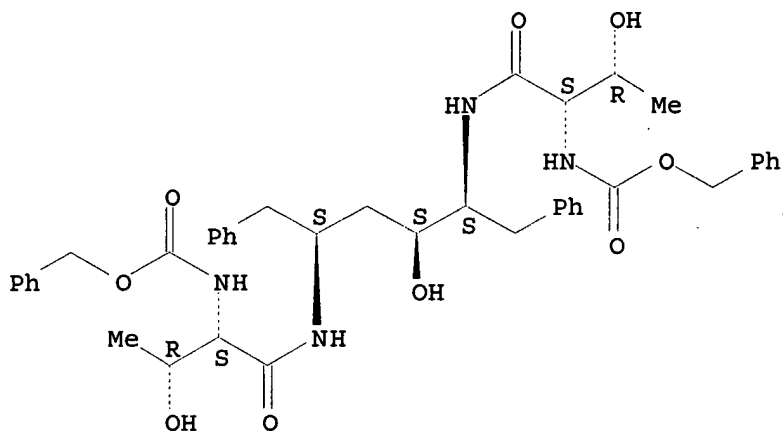
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS

IN 2,5,10,13-Tetraazatetradecanedioic acid, 7-hydroxy-3,12-bis(1-hydroxyethyl)-4,11-dioxo-6,9-bis(phenylmethyl)-, bis(phenylmethyl) ester, [3S-[3R\*(S\*),6R\*,7R\*,9R\*,12R\*(S\*)]]- (9CI)

MF C42 H50 N4 O9

Absolute stereochemistry.

Searcher : Shears 308-4994

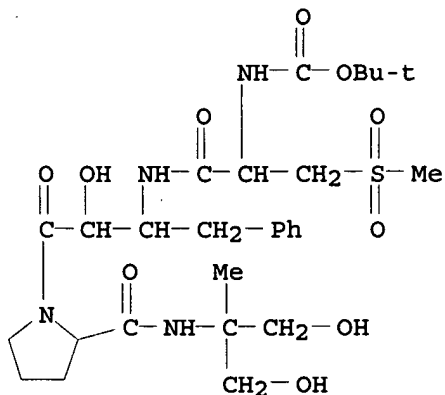


L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS

IN L-Prolinamide, N-[(1,1-dimethylethoxy)carbonyl]-3-(methylsulfonyl)-L-alanyl-(2S,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-N-[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]- (9CI)

SQL 4

MF C28 H44 N4 O10 S

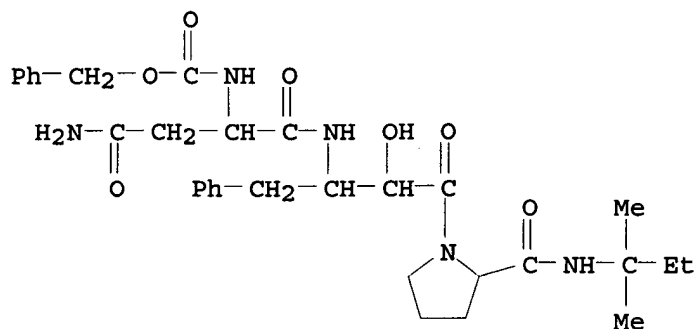


L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS

IN L-Prolinamide, N2-[(phenylmethoxy)carbonyl]-L-asparaginyl-(2S,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-N-(1,1-dimethylpropyl)- (9CI)

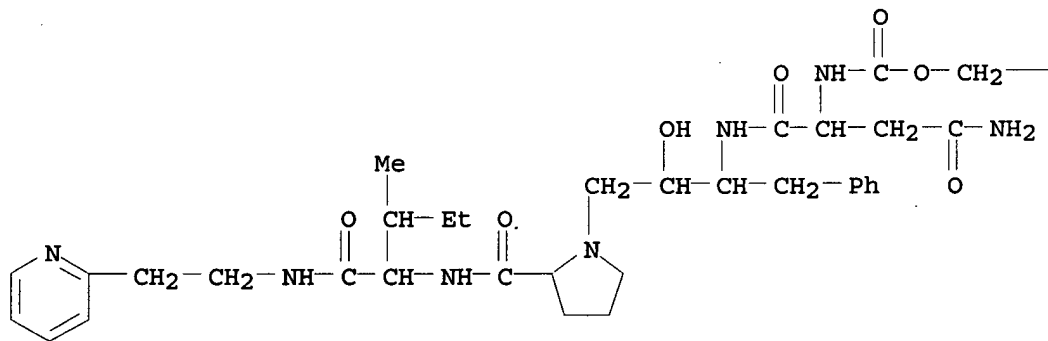
Searcher : Shears 308-4994

MF C32 H43 N5 O7



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS  
 IN L-Isoleucinamide, 1-[3-[[4-amino-1,4-dioxo-2-  
 [(phenylmethoxy) carbonyl]amino]butyl]amino]-2-hydroxy-4-  
 phenylbutyl]-L-prolyl-N-[2-(2-pyridinyl)ethyl]-, [2R-[2R\*,3S\*(S\*)]]-  
 (9CI)  
 MF C40 H53 N7 O7

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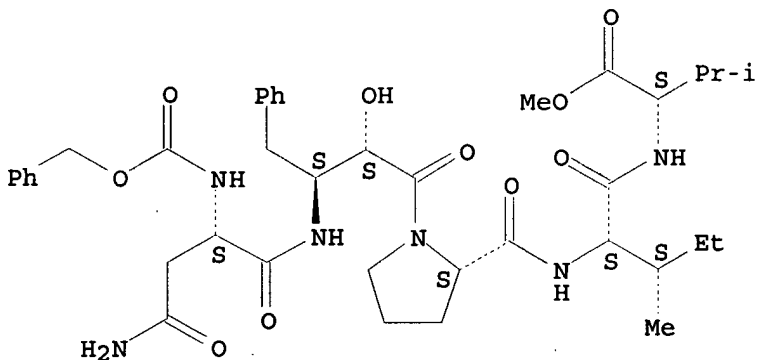
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS  
 Searcher : Shears 308-4994

IN L-Valine, N2-[(phenylmethoxy)carbonyl]-L-asparaginyl-(2S,3S)-2-hydroxy-4-phenyl-3-aminobutanoyl-L-prolyl-L-isoleucyl-, methyl ester (9CI)

SQL 5

MF C39 H54 N6 O10

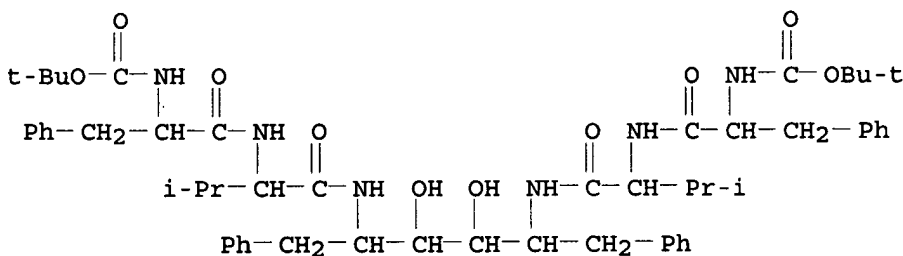
Absolute stereochemistry.



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS

IN L-Iditol, 1,2,5,6-tetra-deoxy-2,5-bis[[N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-valyl]amino]-1,6-diphenyl- (9CI)

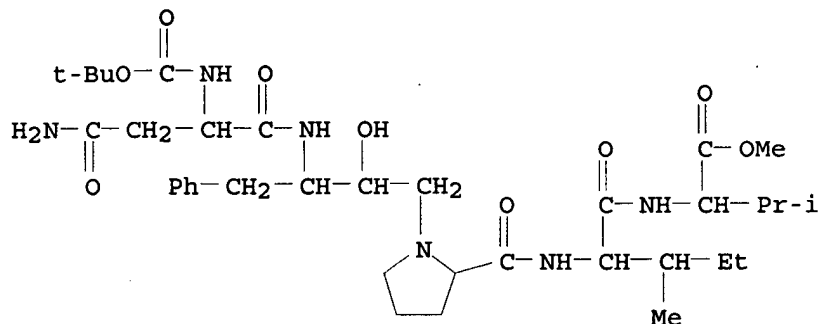
MF C56 H76 N6 O10



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS

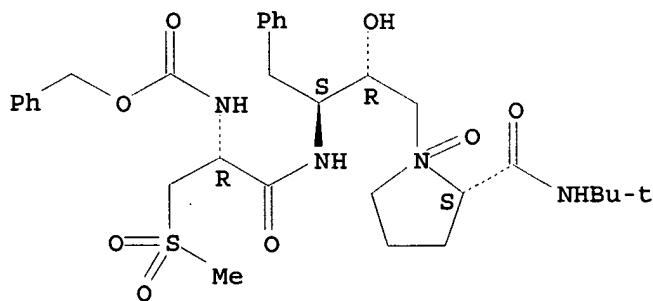
IN L-Valine, N-[N-[1-[3-[[4-amino-2-[[[(1,1-dimethylethoxy)carbonyl]amino]-1,4-dioxobutyl]amino]-2-hydroxy-4-phenylbutyl]-L-prolyl]-L-isoleucyl]-, methyl ester, [2R-[2R\*,3S\*(S\*)]]- (9CI)

MF C36 H58 N6 O9



L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS  
 IN Carbamic acid, [2-[[3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-1-oxido-1-pyrrolidinyl]-2-hydroxy-1-(phenylmethyl)propyl]amino]-1-[(methylsulfonyl)methyl]-2-oxoethyl]-, phenylmethyl ester, [2S-[1[1R\*(S\*),2S\*],2R\*]]- (9CI)  
 MF C31 H44 N4 O8 S

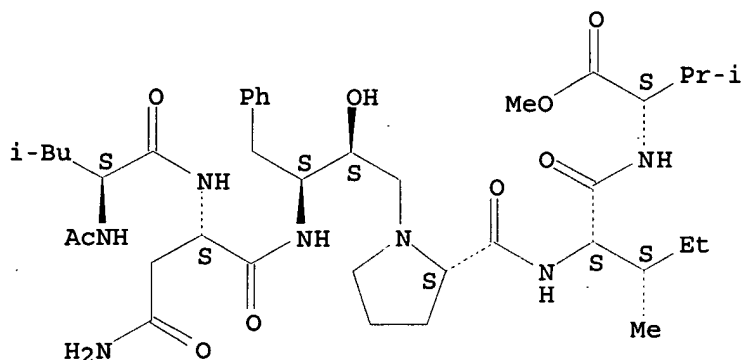
Absolute stereochemistry.



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 IN L-Valine, N-[N-[1-[3-[N2-(N-acetyl-L-leucyl)-L-asparaginyl]amino]-2-hydroxy-4-phenylbutyl]-L-prolyl]-L-isoleucyl]-, methyl ester, [S-(R\*,R\*)]- (9CI)  
 SQL 6  
 MF C39 H63 N7 O9

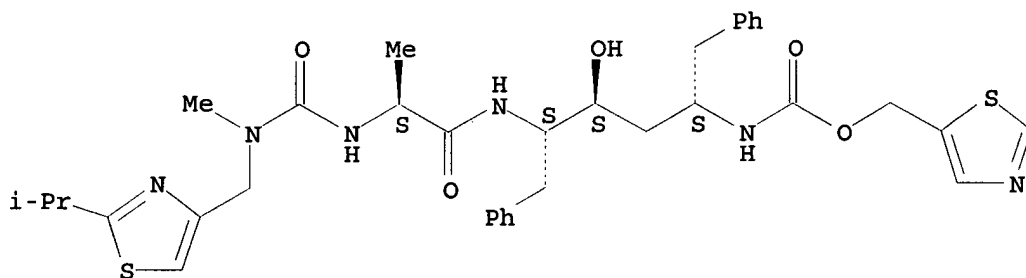
Absolute stereochemistry.





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 IN 2,4,7,12-Tetraazatridecan-13-oic acid, 9-hydroxy-2,5-dimethyl-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, [5S-(5R\*,8R\*,9R\*,11R\*)] - (9CI)  
 MF C35 H44 N6 O5 S2

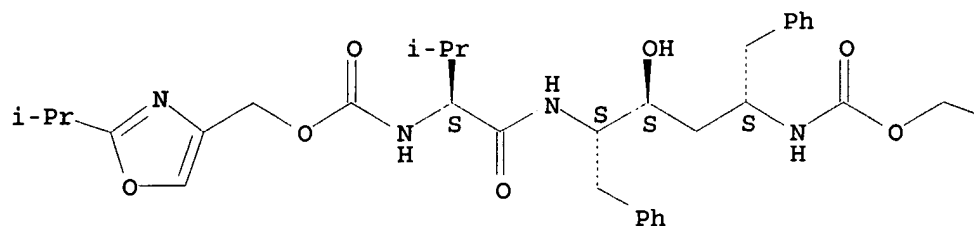
Absolute stereochemistry.



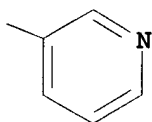
L15 943 ANSWERS REGISTRY COPYRIGHT 1999 ACS  
 IN 2-Oxa-4,7,12-triazatridecan-13-oic acid, 9-hydroxy-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-oxazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 3-pyridinylmethyl ester, [5S-(5R\*,8R\*,9R\*,11R\*)] - (9CI)  
 MF C38 H47 N5 O7

Absolute stereochemistry.

PAGE 1-A

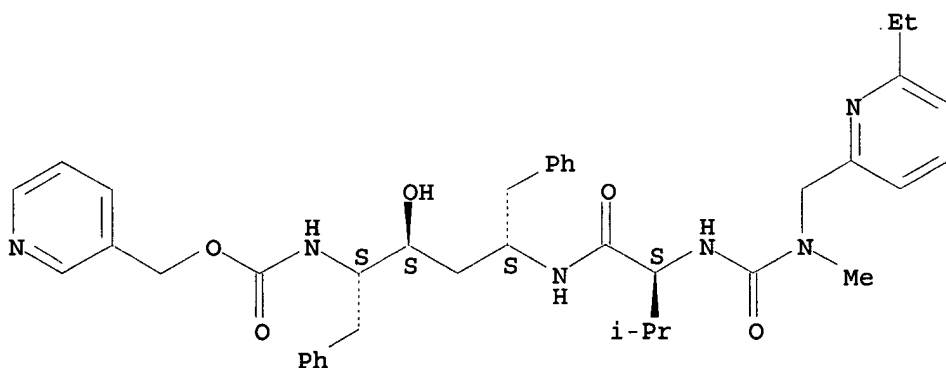


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 IN 2,4,7,12-Tetraazatridecan-13-oic acid, 1-(6-ethyl-2-pyridinyl)-10-hydroxy-2-methyl-5-(1-methylethyl)-3,6-dioxo-8,11-bis(phenylmethyl)-, 3-pyridinylmethyl ester, [5S-(5R\*,8R\*,10R\*,11R\*)]-(9CI)  
 MF C40 H50 N6 O5

Absolute stereochemistry.



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